



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 4, 16, 201, 210, 211, 213, 230, 314, and 514

[Docket No. FDA-2021-N-1333]

RIN 0910-AH96

Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing new regulations that would amend the requirements concerning current good manufacturing practice (CGMP) and postmarketing safety reporting that apply to certain medical gases. FDA further proposes to establish regulations regarding certification of designated medical gases and amend the labeling regulations that apply to certain medical gases. This action, if finalized, will clarify the regulatory obligations of entities that manufacture, process, pack, label, or distribute certain medical gases, as well as reduce regulatory burden in this area. This proposed rule is intended to establish requirements that are more specifically tailored to the medical gas industry.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit written comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL*

REGISTER]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2021-N-1333 for “Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Submit comments on information collection issues under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at <https://www.reginfo.gov/public/do/PRAMain>. Find these particular information collections by selecting “Currently under Review - Open for Public Comments” or by using the search function. The titles of the proposed collections are:

- Current Good Manufacturing Practice (CGMP): Manufacturing, Processing, Packing, and Holding of Drugs; GMP for Finished Pharmaceuticals (Including Medical Gases and Active Pharmaceutical Ingredients); OMB control number 0910-0139--Revision
- Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products; OMB control number 0910-0572--Revision
- Current Good Manufacturing Practice for Medical Gases; OMB control number for 21 CFR part 213--New
- Certification and Postmarketing Reporting for Designated Medical Gases; OMB control number for 21 CFR part 230--New

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule:* David Faranda, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-8767, David.Faranda@fda.hhs.gov.

With regard to the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRASStaff@fda.hhs.gov.

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I. Executive Summary

A. Purpose of the Proposed Rule

Section 756 of the Consolidated Appropriations Act, 2017 (Pub. L. 115-31) required FDA to issue final regulations revising the Federal drug regulations with respect to medical gases by July 15, 2017. These proposed regulations, if finalized, would satisfy that requirement and are intended to be more specifically tailored to the medical gas industry and decrease regulatory burden where appropriate.

FDA proposes revisions to its labeling regulations to provide clarity and consistency regarding how information is presented in the labeling of certain medical gases, as well as to ensure important safety information is included. FDA also proposes new CGMP regulations for medical gases to reflect appropriate requirements for the manufacturing, processing, packing, and holding of such products. These proposed regulations generally cover the same categories of provisions as the CGMP regulations in parts 210 and 211 (21 CFR parts 210 and 211) (hereafter the “general drug CGMP regulations”), revised as appropriate for medical gases. FDA also proposes regulations that would implement and clarify the certification process for designated medical gases described in section 576 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360ddd-1). Lastly, FDA proposes new postmarketing safety reporting regulations for designated medical gases that would address human and animal use and would better reflect the development, manufacturing, and distribution of designated medical gases.

B. Summary of the Major Provisions of the Proposed Rule

1. Labeling Provisions

This proposed rule includes several proposed changes to FDA’s drug labeling regulations including adding certain operations required to produce a medical gas to the list of operations that are performed by its manufacturer. We propose to revise the requirements for stating the ingredients in the labeling of a designated medical gas or medically appropriate combination of designated medical gases (referred to hereafter in this preamble as “medically appropriate

combination”).¹ We propose to specify requirements for the declaration of net quantity of contents in the labeling of designated medical gases and medically appropriate combinations.

We propose that all designated medical gases--whether certified for human use, animal use, or both--and medically appropriate combinations bear labeling that is in a standardized format.

FDA further proposes revisions to warning statements for certain medical gases including that the labeling of medical air and carbon monoxide bear certain warning statements. We propose different labeling requirements for final use containers and bulk or transport containers. We also propose a new oxygen warning statement and graphic warning symbol to alert users of the risks of smoking, vaping, and open flames near an oxygen container.

FDA proposes revisions to the medical gas container labeling regulations to clarify that the owner of a designated medical gas container or a container of a medically appropriate combination can be mentioned on the container to facilitate return of the container to the owner, and to ensure that product quality issues are directed to the appropriate entity.

2. CGMP Provisions

FDA proposes CGMP regulations specific to medical gases. These proposed regulations include many of the same categories of provisions as the general drug CGMP regulations but reflect differences in how medical gases are manufactured, processed, packed, and held. If finalized as proposed, these regulations would represent the minimum CGMP for medical gases. Of note, we propose different cleaning requirements for medical gases because these gases are generally manufactured in a sealed, closed system, and because cleaning at inappropriate times

¹ Section 576(a)(3)(A)(i) of the FD&C Act provides that “[a] designated medical gas for which a certification is granted under paragraph (2) is deemed, alone or in combination, as medically appropriate, with another designated medical gas or gases for which a certification or certifications have been granted, to have in effect an approved application under section 505 or 512, subject to all applicable postapproval requirements,” for certain indications for use. FDA interprets the term “combination” in this section to mean two or more distinct designated medical gases that are mixed together. For example, a mixture of oxygen and nitrous oxide that each meet the standards set forth in an official compendium could constitute a medically appropriate combination of designated medical gases. However, the addition of oxygen to a container that already contains oxygen would not result in a medically appropriate combination of designated medical gases because only one kind of designated medical gas would be present in the container.

can introduce contaminants. Additionally, FDA proposes requirements for medical gas containers and closures that are similar to the general drug CGMP regulations, with an additional proposed requirement that portable cryogenic medical gas containers and small cryogenic gas containers for use by individual patients have a working gauge to indicate whether there is an adequate supply of gas for continued use. This would help users determine when a container must be refilled or replaced and when a leaking or venting container is empty. We are also not proposing to include time limitations on production because medical gases are generally not expected to expire or degrade. FDA also proposes that, unlike the salvaging requirements under the general drug CGMP regulations, medical gases that have been stored improperly may be salvaged unless their containers have been subjected to adverse conditions that negatively impact the identity, strength, quality, or purity of the product or the integrity of the product's container closure.

3. Certification Provisions

FDA proposes regulations regarding the certification process for designated medical gases that are intended to codify the certification process and provide additional clarity where necessary. These proposed requirements would govern the process for applicants to file a certification request and supplements as well as the contents of such a request. The regulations would set forth requirements concerning the transfer of ownership of a certification from one entity to another.

We are proposing to require the submission of a streamlined annual report, including the required contents and timing for submission.

These proposed regulations would set forth requirements that are similar to the recommendations described in the November 2015 draft guidance for industry "Certification Process for Designated Medical Gases" (November 25, 2015, 80 FR 73771) (Ref. 1).

4. Postmarketing Safety Reporting Provisions

FDA is proposing new postmarketing safety reporting regulations for designated medical gases and general safety reporting requirements for all certified designated medical gases.

We also propose adverse event reporting requirements related to the use of designated medical gases in humans and animals. For designated medical gases that are certified for human use and deemed to have in effect an approved application under section 505 of the FD&C Act (21 U.S.C. 355), we are proposing that applicants and nonapplicants be required to report serious adverse events within 15 calendar days from when the applicant or nonapplicant has both met certain reporting criteria and acquired certain minimum data.

We are also proposing requirements for the contents and format of submissions, including an electronic submission requirement, the process for requesting a waiver of the electronic submission requirement, recordkeeping requirements, written procedures requirements, and patient privacy provisions.

For designated medical gases that are certified for animal use and deemed to have in effect an approved application under section 512 of the FD&C Act (21 U.S.C. 360b), we are proposing that applicants and nonapplicants be required to submit serious adverse event reports to FDA within 15 calendar days from when the applicant or nonapplicant has met certain reporting criteria and that recordkeeping requirements related to adverse events are maintained.

C. Legal Authority

Sections 501, 502, 505, 512, 575, 576, and 704 of the FD&C Act (21 U.S.C. 351, 352, 355, 360b, 360ddd, 360ddd-1, and 374), in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)) serve as our principal legal authority for this proposed rule.

D. Costs and Benefits

The costs of this proposed rule, if finalized, would be primarily driven by new labeling requirements, regulatory clarification leading to firms becoming compliant with existing

requirements, and added CGMP requirements including a requirement for portable cryogenic containers to have a working gauge. The cost savings of this proposed rule, if finalized, would be primarily driven by removing CGMP requirements that would not apply to medical gases, such as removing certain building and facility requirements, or modifying CGMP requirements so that they would be more well-tailored to medical gases, which may streamline inspections. The annualized benefits are estimated to be \$3.24 million at a 7 percent discount rate over 10 years. The annualized costs are estimated to be \$3.03 million at a 7 percent discount rate over 10 years.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
API	Active Pharmaceutical Ingredient
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
CVM	Center for Veterinary Medicine
FAR	Field Alert Report
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA or Agency	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FR	<i>Federal Register</i>
ICSR	Individual Case Safety Report
NDA	New Drug Application
NADA	New Animal Drug Application
NF	National Formulary
OMB	Office of Management and Budget
PRIA	Preliminary Regulatory Impact Analysis
USP	United States Pharmacopeia

III. Background

A. Introduction

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA, Pub. L. 112-144) was signed into law, establishing a new marketing pathway and specific requirements for the regulation of designated medical gases. Section 756 of the Consolidated

Appropriations Act, 2017, required FDA to issue final regulations revising the Federal drug regulations with respect to medical gases by July 15, 2017.

The Agency has engaged with stakeholders and Congress to evaluate the need for changes to regulatory requirements for medical gases. This proposed rule is being published to address the areas for which FDA has determined regulatory changes are needed.

B. Need for the Regulation

Medical gases have historically been manufactured, labeled, and distributed in a manner different than most other drugs. Under section 576 of the FD&C Act, the process for obtaining marketing authorization for a designated medical gas also differs from the process for obtaining marketing authorization for other human and animal drugs. Moreover, because of these differences, sponsors of designated medical gases do not generate the same safety information that sponsors of new drug applications (NDAs) and new animal drug applications (NADAs) would typically generate, including, for example, an understanding of expected adverse events based on clinical trial data. Thus, some existing regulations are not well-tailored to addressing designated medical gases and other medical gases. FDA is undertaking this rulemaking to address these differences, and to decrease regulatory burden where appropriate.

C. FDA's Current Regulatory Framework

Section 1111 of FDASIA established sections 575 through 577 of the FD&C Act (21 U.S.C. 360ddd through 360ddd-2) for medical gases. Section 575(2) of the FD&C Act defines a medical gas as a drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state and administered as a gas. Section 575(1) of the FD&C Act defines a designated medical gas as any of the following gases that meet the standards set forth in an official compendium: oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air. Designated medical gases are also defined to include any other medical gas deemed appropriate by the Secretary of the Department of Health and Human Services (Secretary),² after taking into

² The functions of the Secretary described herein have been delegated to FDA.

account any investigational new drug application or investigational new animal drug file³ for the same medical gas submitted in accordance with applicable regulations, unless any period of exclusivity for a new drug under section 505(c)(3)(E)(ii) or (j)(5)(F)(ii) of the FD&C Act, or the extension of any such period under section 505A of the FD&C Act (21 U.S.C. 355a) , or any period of exclusivity for a new animal drug under section 512(c)(2)(F) of the FD&C Act, applicable to such medical gas has not expired (section 575(1)(H) of the FD&C Act).

Any person who seeks to initially introduce or deliver for introduction into interstate commerce a designated medical gas may file with the Secretary a request for certification of a medical gas as a designated medical gas (FD&C Act section 576(a)(1)). Any such request shall contain a description of the medical gas, the sponsor's name and address, the name and address of the facility or facilities where the medical gas is or will be manufactured, and any other information the Secretary deems appropriate to determine whether the medical gas is a designated medical gas (Id.). The certification requested under section 576(a)(1) of the FD&C Act is deemed to be granted unless, within 60 days of filing of the request, the Secretary finds that the medical gas subject to the certification is not a designated medical gas, the request does not contain the information required under section 576(a)(1) of the FD&C Act or otherwise lacks sufficient information to permit the Secretary to determine that the medical gas is a designated medical gas, or denying the request is necessary to protect the public health (FD&C Act section 576(a)(2)). FDA interprets the period of 60 days in section 576(a)(2) to mean a period of 60 calendar days.

Section 576(a)(3)(A)(i) of the FD&C Act provides that a designated medical gas for which a certification is granted is deemed, alone or in combination, as medically appropriate, with another designated medical gas or gases for which a certification or certifications have been granted, to have in effect an approved application under section 505 or 512 of the FD&C Act,

³ We interpret the term “investigational new animal drug application” in FD&C Act section 575(1)(H) to refer to an “investigational new animal drug file” to reflect CVM’s current administrative process for receiving data and information related to a new animal drug for investigational use. See 21 CFR part 511.

subject to all applicable postapproval requirements. The deemed approval is for certain indications specified in the statute or for any other indication for use for a designated medical gas or combination of designated medical gases deemed appropriate by the Secretary, unless any period of exclusivity under section 505(c)(3)(E)(iii) or (iv), 505(j)(5)(F)(iii) or (iv), or 527 of the FD&C Act (21 U.S.C. 360cc), or the extension of any such period under section 505A of the FD&C Act, applicable to such indication for use for such gas or combination of gases has not expired. Under section 576(a)(3)(A)(ii) of the FD&C Act, designated medical gases are deemed to have met the requirements of section 503(b)(4) of the FD&C Act (21 U.S.C. 353(b)(4); concerning the labeling of drugs with the symbol “Rx only”) and section 502(f) of the FD&C Act (concerning the labeling of drugs with adequate directions for use and adequate warnings against certain uses) if the labeling on the final use container bears:

- The information required by section 503(b)(4) of the FD&C Act;
- A warning statement concerning the use of the medical gas as determined by the Secretary by regulation; and
- Appropriate directions and warnings concerning storage and handling.

Designated medical gases that are deemed to have in effect an approved application under section 576(a)(3)(A)(i) of the FD&C Act are not eligible for any period of exclusivity for a new drug under section 505(c) or (j), or 527 of the FD&C Act, or the extension of any such period under section 505A of the FD&C Act, on the basis of such deemed approval (FD&C Act section 576(a)(3)(B)(i)). In addition, no period of exclusivity under section 505(c), 505(j), or 527 of the FD&C Act, or the extension of any such period under section 505A of the FD&C Act, with respect to an application for a drug product, shall prohibit, limit, or otherwise affect the submission, grant, or effect of a designated medical gas certification, except as provided in sections 575(1)(H) and 576(a)(3)(A)(i)(VIII) of the FD&C Act (FD&C Act 576(a)(3)(B)(ii)).

Section 576(a)(4)(A) of the FD&C Act affirms the Secretary’s authority to withdraw or suspend approval of a drug product, including a designated medical gas deemed to have in effect

an approved application under section 505 or 512 of the FD&C Act. The Secretary under section 576(a)(4)(B) of the FD&C Act may revoke the grant of a designated medical gas certification upon the determination that the certification request contains any material omission or falsification.

Under section 576(b)(1) of the FD&C Act, designated medical gases are subject to the requirements under section 503(b)(1) of the FD&C Act (concerning the dispensing of certain human drugs only pursuant to a prescription) except under the following circumstances:

- The Secretary exercises the authority provided in section 503(b)(3) of the FD&C Act to remove the designated medical gas from the requirements of section 503(b)(1) of the FD&C Act;
- The gas is approved for use without a prescription pursuant to an application under section 505 or 512 of the FD&C Act; or
- The use in question is authorized pursuant to another provision in the FD&C Act relating to the use of medical products in emergencies.

Notwithstanding section 576(b)(1), section 576(b)(2)(A) of the FD&C Act provides that oxygen may be provided without a prescription for use in the event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel. For oxygen provided without a prescription, section 576(b)(2)(B) provides that the requirements of section 503(b)(4) (concerning labeling of drugs with the symbol “Rx only”) are deemed to have been met if its labeling bears a warning that it can only be used for emergency use, and that for all other medical applications a prescription is required.

Pursuant to section 577 of the FD&C Act, a designated medical gas, alone or in a medically appropriate combination with another designated medical gas or gases deemed under section 576 to have in effect an approved application, shall not be assessed prescription drug user

fees under section 736(a) of the FD&C Act (21 U.S.C.379h(a)) or animal drug user fees under section 740(a) of the FD&C Act (21 U.S.C. 379j-12(a)) on the basis of such deemed approval.

FDA's drug regulations also include several requirements specific to medical gases. FDA labeling regulations under part 201 (21 CFR part 201) that currently address the labeling of medical gases include the following:

- Section 201.25(b)(1)(i)(D), which exempts medical gases from bar code label requirements that otherwise apply to human prescription drug products;
- Section 201.161, which exempts certain medical gases from specified requirements if, among other things, applicable warning statements and information concerning storage and handling are included in the labeling; and
- Section 201.328, which describes certain labeling requirements for portable cryogenic medical gas containers and high-pressure medical gas cylinders, including a color coding system.

FDA's CGMP regulations under parts 210 and 211 that currently specifically address the manufacturing, labeling, and containers and closures for medical gases include the following:

- Section 211.94(e), which provides container and closure requirements for medical gases, including gas-specific outlet connections and label and coloring requirements;
- Section 211.125(c), which waives labeling reconciliation requirements for 360° wraparound labels on portable cryogenic medical gas containers;
- Section 211.170(b), which exempts compressed medical gases from the requirement to retain reserve samples; and
- Section 211.196, which exempts compressed medical gas products from the requirement that distribution records contain lot or control numbers.

D. History of the Rulemaking

In developing this proposed rule, FDA held three public workshops (Ref. 2), on December 15, 2017, February 9, 2018, and May 11, 2018, and opened a docket for public

comment (FDA-2018-N-1214).⁴ The Agency received several comments from interested stakeholders during the public workshops and received more than a dozen comments through the docket. Additionally, FDA received one comment in relation to its regulatory reform efforts associated with Executive Orders 13771 and 13777 (FDA-2017-N-5093).⁵ Comments were submitted by industry groups, individual manufacturers, and private citizens. FDA has considered these comments in developing this proposed rule.

FDA received comments recommending revisions to requirements that commenters believe are not well-tailored to medical gases. Other comments addressed safety and handling concerns for medical gases. Multiple comments discussed whether FDA should add additional gases to the list of designated medical gases. Finally, some comments addressed other uses for certain medical gases.

IV. Legal Authority

Sections 501, 502, 505, 512, 575, 576, 701, and 704 of the FD&C Act provide the principal legal authority for this proposed rule. Medical gases are generally regulated as prescription drugs under sections 201(g)(1) and 503(b)(1) of the FD&C Act (though oxygen may be provided without a prescription for certain uses specified at section 576(b)(2) of the FD&C Act).

Section 501 of the FD&C Act describes the circumstances under which a drug is deemed to be adulterated. Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. For purposes of section 501(a)(2)(B), “current good manufacturing practice” includes the implementation of oversight and controls

⁴ The announcement for the first two workshops referenced Docket No. FDA-2017-N-0001 (82 FR 54353, November 17, 2017). In the announcement for the third workshop, FDA announced that the docket number would change to FDA-2018-N-1214 and that all comments submitted to the first docket would be transferred to the new docket number (83 FR 13440, March 29, 2018).

⁵ These Executive Orders were revoked by Executive Order 13992.

over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products. Section 502 of the FD&C Act describes the circumstances under which a drug is deemed to be misbranded. Under section 502(f) of the FD&C Act, a drug is deemed to be misbranded unless its labeling bears adequate directions for use and such adequate warnings against use where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration, in such manner and form, as are necessary for the protection of users. Under section 704 of the FD&C Act, FDA is authorized to inspect, among other things, records in any establishment in which prescription drugs or nonprescription drugs intended for human use are manufactured, processed, packed, or held bearing on whether such products are in violation of the FD&C Act.

Section 576 of the FD&C Act describes the certification process for designated medical gases (as defined in section 575 of the FD&C Act) and the effect of certification, the applicability of FDA's prescription requirements, and certain labeling requirements. Under section 576(a)(3)(A)(i), a certified designated medical gas is subject to all applicable postapproval requirements. Under section 505(k) of the FD&C Act, FDA has the authority to establish certain postmarketing safety reporting regulations for human drugs to enable FDA to determine or facilitate a determination as to whether there are or may be grounds to invoke section 505(e) of the FD&C Act, which concerns the withdrawal or suspension of approval of an NDA or abbreviated new drug application (ANDA). Section 512(l) of the FD&C Act authorizes FDA to establish postmarketing safety reporting regulations for new animal drugs to enable FDA to determine or facilitate a determination as to whether there are or may be grounds to withdraw approval of an application pursuant to section 512(e) or 512(m)(4) of the FD&C Act.

Thus, sections 501, 502, 505, 512, 575, 576, and 704 of the FD&C Act, in conjunction with our general authority in section 701(a) of the FD&C Act to promulgate regulations for the

efficient enforcement of the FD&C Act, serve as our principal legal authority for this proposed rule.

V. Description of the Proposed Rule

We are proposing to establish new parts 213 and 230 (21 CFR parts 213 and 230) and amend parts 4, 16, 201, 210, 211, 314, and 514 (21 CFR parts 4, 16, 201, 210, 211, 314, and 514). The proposed rule would:

- Revise the labeling regulations specific to medical gases;
- Establish CGMP requirements specific to medical gases;
- Establish regulations governing the designated medical gas certification process under section 576 of the FD&C Act, including certain postapproval requirements; and
- Establish postmarketing safety reporting requirements specific to designated medical gases.

A. Proposed Labeling Provisions

FDA proposes revisions to the labeling regulations in part 201 related to medical gases.

1. Definitions

Proposed § 201.161(c)(1) defines the term “designated medical gas.” This definition refers to the statutory definition found in section 575(1) of the FD&C Act and is intended to apply to the same gases described in section 575(1) of the FD&C Act.

The term “final use container” is defined in proposed § 201.161(c)(2) to mean a container that is for direct use or access by a patient or healthcare provider to administer a designated medical gas or medically appropriate combination of designated medical gases. The following would not be included in the proposed definition of “final use container”:

- bulk or transport containers, or
- containers described in § 868.5655 (21 CFR 868.5655).

The Agency specifically requests comment on the scope of the proposed definition of “final use container” and how it relates to current labeling practice.

The term “bulk or transport container” is defined in proposed § 201.161(c)(3) to mean a container used to transport or store designated medical gases or medically appropriate combinations of designated medical gases and that is not used directly to administer such gases to a patient. This definition would cover storage tanks, storage banks, railcars, and tanker trucks. It would also include containers that are connected to medical gas supply systems (for example, cylinders connected to a hospital’s oxygen system).

2. Description of Proposed Provisions

In § 201.1(b), FDA proposes to add certain operations that are required to produce a medical gas to the list of operations that are performed by its manufacturer for purposes of section 502(a) and (b)(1) of the FD&C Act and as used in the Agency’s labeling regulations in part 201. FDA proposes that fabricating a medical gas by chemical reaction, physical separation, compression of atmospheric air, purification (e.g., reprocessing an industrial gas into a medical gas), by combining two or more distinct medical gases, or by other process, would constitute an operation performed by a manufacturer. Medical gases are produced via several different processes, including air separation, chemical synthesis, and compression, and FDA believes the proposed language would address all such processes. However, under the proposed language, repacking or filling operations in which a finished medical gas is transferred from one container to another, including a container that contains the same medical gas (sometimes referred to as transfilling or “curbside filling” activities at the point of use), would not be considered an operation performed by a manufacturer for purposes of the labeling regulations in part 201 (note that transfilling would be considered a manufacturing activity for purposes of the proposed CGMP regulations under part 213), so long as those operations are limited to transferring finished gas from one container to another without any change or transformation of the gas. FDA also notes that this provision refers to “medical gas” instead of “designated medical gas” because the processes used to produce designated medical gases and other types of medical gases generally fit within the broad categories of processes described in the proposed language. The

Agency believes that clarification is needed for all medical gases, and as such, FDA proposes to list operations that are required to produce a medical gas as operations that are performed by its manufacturer, regardless of whether the medical gas is a designated medical gas.

FDA proposes to revise § 201.10(d)(2) to specify the format for a statement of ingredients for designated medical gases. FDA proposes that the statement of the percentage of a designated medical gas in a drug product be expressed in percent volume/volume. The intent of this provision is to better clarify and consistently display the amount of each designated medical gas present in a container.

FDA proposes to revise § 201.51, which requires the label of a prescription drug in package form to bear a declaration of net quantity of contents. In paragraph (a), FDA proposes to clarify that the statement of quantity of designated medical gases and medically appropriate combinations thereof in a gaseous state shall be in terms of volume measure. In paragraph (b), FDA proposes to clarify that the statement of liquid measure currently described in the regulation would not apply to designated medical gases or medically appropriate combinations thereof. Rather, FDA proposes separate requirements for the declaration of net quantity in the labels of designated medical gases or medically appropriate combinations thereof in a:

- Gaseous state in a high-pressure container;
- Liquefied compressed gas state in a high-pressure container; or
- Liquefied state in a portable cryogenic container.

FDA recognizes that some reasonable level of product loss due to venting or evaporation is expected during manufacture; thus, minor deviations between the stated net quantity and the actual net quantity that result from normal venting over time would not cause the product to be misbranded. FDA believes that the information in 201.51(b)(1) through (3) can be included on a separate sticker or decal on the container, and need not be contiguous with other portions of required labeling. Under proposed § 201.51(b)(4), labeling for net quantity of contents is not

required for bulk or transport containers, as defined in § 201.161(c)(3). Examples of such containers include storage tanks, storage banks, railcars, and tanker trucks.

FDA proposes that designated medical gases and medically appropriate combinations for animal use utilize the same labeling information as designated medical gases and medically appropriate combinations for human use. Accordingly, FDA proposes to amend § 201.105 to exempt designated medical gases and medically appropriate combinations from the misbranding requirements of section 502(f)(1) of the FD&C Act if they are in compliance with the labeling requirements of § 201.161. This proposal is intended to allow manufacturers to have one set of labeling that can be utilized for both human and animal use of their designated medical gases. Manufacturers will not necessarily know at the time of manufacture, filling, or distribution how their gas will be used. Additionally, FDA expects that requiring two separate sets of labeling would create a significant burden on industry with little or no benefit to product safety or patient outcomes. Because FDA is not aware of any reason to require different information for animal use, the Agency believes utilization of the same labeling for both human and animal use is appropriate.

FDA proposes several revisions to § 201.161 in addition to the proposed definitions described above. Under proposed paragraph (a), the requirements of section 503(b)(4) (concerning when a drug's label must bear the symbol "Rx only") and 502(f) (requiring a drug's labeling to bear adequate directions for use and certain adequate warnings) of the FD&C Act are deemed to have been met for a designated medical gas or a medically appropriate combination of designated medical gases if the labeling on its final use container bears certain information depending on the specific gas or gases it contains. Each of the proposed revisions is described in turn below.

FDA proposes revisions to the statement describing the effect of compliance with this section. FDA proposes this revision to more closely align with section 576(a)(3)(A)(ii) of the FD&C Act. FDA does not believe it is necessary for § 201.161(a) to include exemptions from 21

CFR 201.100(b)(2), (3), and (c)(1), given that section 576(a)(3)(A)(ii) of the FD&C Act provides a separate way of satisfying the requirements of section 502(f) for designated medical gases.

FDA proposes to remove the list of gases in § 201.161(a) and instead refer to “designated medical gas.” FDA proposes these revisions to § 201.161 for consistency with section 576(a)(3)(A)(ii) of the FD&C Act. The proposed revisions would bring medical air and carbon monoxide that meet the definition of “designated medical gas” within the scope of § 201.161; these gases are not included in the list of gases in § 201.161 currently but are designated medical gases for which a certification can be granted under section 576 of the FD&C Act. Instead of adding medical air and carbon monoxide to the list of gases, FDA proposes to revise the first sentence to clarify that all designated medical gases and medically appropriate combinations thereof are within the scope of § 201.161(a). Should other medical gases be added to the definition of “designated medical gas” pursuant to section 575(1)(H) of the FD&C Act in the future, this proposed revision would make the provisions of § 201.161 applicable to such gases without the need to amend this regulation further. This proposed revision would also ensure that all designated medical gases other than oxygen, including medical air and carbon monoxide, and medically appropriate combinations of designated medical gases are required to bear the label statements in proposed § 201.161(a)(2) in order for sections 503(b)(4) and 502(f) to be deemed to be met for such gas or gases.

FDA proposes to remove the language in § 201.161 referencing §§ 201.328 and 211.94(e)(2). FDA believes it is unnecessary for § 201.161 to reference compliance with §§ 201.328 and 211.94(e)(2) as a condition for sections 503(b)(4) and 502(f) to be deemed to be met.

Additionally, FDA proposes to revise paragraph (a) to require that the final use container of a designated medical gas or medically appropriate combination of gases must bear the required information in order for sections 503(b)(4) and 502(f) to be deemed to be met for such gas or gases. This proposed revision is intended to clarify that the warnings, directions, and other

information in § 201.161(a) must appear in the labeling of the final use container of a designated medical gas or medically appropriate combination of designated medical gases in order for the requirements of sections 503(b)(4) and 502(f) of the FD&C Act to be deemed to be met for such gas or gases, consistent with the requirements in section 576(a)(3)(A)(ii) of the FD&C Act.

In the case of oxygen, FDA proposes to require the final use container to bear a warning statement providing the following (§ 201.161(a)(1)(i)):

- uninterrupted use of high concentrations of oxygen over a long duration, without monitoring its effect on oxygen content of arterial blood, may be harmful;
- oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment; and
- in the case of oxygen that may be provided without a prescription for use in the event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel, a warning that the oxygen can be used for emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation, and that for all other medical applications a prescription is required.

This is the same information currently required in § 201.161(a)(1)(i) for oxygen. FDA believes this information is important to convey the risks of using oxygen and is consistent with the requirements in section 576(a)(3)(A)(ii) and (b)(2) of the FD&C Act.

FDA proposes § 201.161(a)(1)(ii), which would require clear and prominent “no smoking” and “no vaping” warning statements and a graphic warning symbol on the label of oxygen final use containers indicating that smoking, vaping, and open flames near oxygen are dangerous. Such a graphic symbol may be based on those created by standards development organizations. FDA is aware of numerous instances of fires related to the medical use of oxygen, most often related to individuals smoking in the vicinity of an oxygen tank in operation.

Additionally, FDA has become aware of some reports that vaping products⁶ have been linked to medical oxygen fires and explosions (Refs. 3 to 6). These events can cause death and serious injury to the patient, as well as cohabitants, neighbors, and first responders. Oxygen cylinders generally contain warnings regarding keeping oil, grease, combustibles, heat, sparks, and flame away from the product (though language varies from cylinder to cylinder). However, this language is generally in very fine print, is not expressed in a manner that is clear to lay users, and does not mention smoking or vaping directly. The purpose of this proposed provision is to include in product labeling a plain-language warning against smoking, vaping, or using open flames near an operating oxygen tank. Because many patients on oxygen therapy have smoking-related illnesses, and because some patients may continue to smoke or vape during treatment, FDA believes that the proposed warning will help mitigate the risk of fires during the administration of oxygen. The proposed “no smoking” and “no vaping” warning statements and graphic symbol may appear on a separate sticker or decal displaying the information on the container or be painted directly on the container. The Agency will continue to consider other risks of combustion as well.

In the case of all designated medical gases other than oxygen, and in the case of medically appropriate combinations of designated medical gases, FDA proposes to require the final use container to bear the following information (§ 201.161(a)(2)(i) and (ii)):

- a warning statement providing that the administration of the gas or gas combination (as applicable) may be hazardous or contraindicated; and
- a warning statement providing that the gas or gas combination (as applicable) should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of the gas or gas combination (as applicable) and is familiar with

⁶ The term “vaping products” includes vapes or vape pens, personal vaporizers, e-cigarettes, cigalikes, e-pens, e-hookahs, e-cigars, e-pipes and other battery-operated tobacco products in addition to other non-nicotine vape products.

the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken.

This is the same information currently required in § 201.161(a)(1)(ii) for the listed gases other than oxygen, as well as for medically appropriate combinations of the listed gases. In addition, FDA proposes to require that the labeling on the final use container of designated medical gases other than oxygen and medically appropriate combinations of designated medical gases bear the symbol “Rx only.” FDA believes this information is important to convey the risks of using these gases and is consistent with the requirements in section 576(a)(3)(A)(ii) and (b)(1) of the FD&C Act.

Under proposed § 201.161(a)(3), the labeling on the final use container for all designated medical gases and medically appropriate combinations thereof would be required to bear appropriate directions and warnings concerning storage and handling. FDA believes this proposed revision is consistent with the current requirement in § 201.161(a)(2). The Agency proposes this revision to reflect the language in section 576(a)(3)(A)(ii)(III) of the FD&C Act on this issue.

The Agency has received comments recommending that it issue a separate warning statement requirement for medical air that states that medical air may be used without a prescription for breathing support when administered by properly trained personnel. FDA has decided not to propose a warning statement for medical air that is different from the warning statement proposed for designated medical gases other than oxygen, nor does FDA otherwise propose to exercise its authority under section 503(b)(3) of the FD&C Act to remove medical air from the requirements of section 503(b)(1). In the 2016 final rule entitled “Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements,” FDA responded to comments asserting that certain non-prescription uses of medical air are medically appropriate by deciding not to finalize its proposal to add medical air to the list of gases at § 201.161(a) and stating that it would continue to consider what would constitute an appropriate warning statement

for medical air (81 FR 81685 at 81689; November 18, 2016). Since the publication of the 2016 final rule, FDA has continued to consider this issue, and the Agency remains unaware of any uses for medical air that would be appropriate for nonprescription use, and no new information supporting such uses has been provided since the Agency last addressed this issue in a citizen petition response to the Compressed Gas Association (Ref. 7). FDA believes that medical air intended for use by properly trained personnel in a healthcare setting should remain a prescription use subject to the requirements of section 503(b)(1) of the FD&C Act. The Agency specifically requests comment on this issue.

Proposed new § 201.161(b) would create separate labeling requirements for bulk or transport containers used for designated medical gases or medically appropriate combinations of designated medical gases. FDA proposes to require that such containers be identified with the name of the product contained therein and be accompanied by documentation identifying the product as meeting applicable compendial standards. As discussed in this section, bulk or transport containers are excluded from the proposed definition of final use containers. Because these large containers are generally removed from the point of care and are not expected to be used directly to administer a designated medical gas or medically appropriate combination of designated medical gases to a patient, FDA does not believe that such containers need to bear the information that would be required under proposed § 201.161(a). However, it is essential that the identity of the gas or gases inside such containers is evident to individuals handling and transporting the containers in order to prevent mix-ups. Many firms in the supply chain for medical gases, including those firms downstream from the manufacturers that initially produce the gas, receive and distribute gases for medical and non-medical use, and some non-medical gases may not meet compendial standards applicable to designated medical gases. Therefore, this proposal would require that a bulk or transport container bears the name of the designated medical gas or medically appropriate combination of designated medical gases contained therein, and that the accompanying documentation identifies that the product meets applicable

compendial standards. These proposed requirements are expected to help prevent mix-ups and ensure that recipients of designated medical gases or medically appropriate combinations thereof in bulk or transport containers are provided information indicating that such gases meet applicable compendial standards.

In § 201.328(a)(1), FDA proposes technical changes to reflect that the requirements in § 211.94(e)(2) are proposed to be moved to § 213.94(e)(3). See section V.B.1 for more information on this proposed revision.

Proposed new § 201.328(d) would provide that the owner of a designated medical gas container or a container of a medically appropriate combination of designated medical gases may be identified on the container. This statement may appear on a separate sticker or decal on the container and need not be contiguous with other labeling on the container, but if the container owner is not the manufacturer, packer, or distributor of the gas, that shall be clearly stated. FDA recognizes the complex distribution system for designated medical gases and medically appropriate combinations of designated medical gases and the importance of allowing container owners to be clearly identified so that patients and healthcare professionals can contact the container owners if necessary. This provision is intended to help ensure that appropriate entities can be contacted regarding quality issues or adverse events. It is additionally intended to facilitate the return of cylinders to owners that may not also be medical gas manufacturers. The proposed inclusion of the container owner's information would not cause the container owner to be a "relabeler" for purposes of FDA's registration and listing requirements.

B. Proposed Current Good Manufacturing Practice Provisions

FDA proposes the establishment of part 213, which would contain the CGMP requirements for preparation of medical gases, including designated medical gases, for administration to humans or animals. If finalized as proposed, medical gases proposed to be subject to part 213 would no longer be subject to part 211. FDA also proposes conforming edits to part 210 so that applicable provisions would reflect the new CGMP regulations for medical

gases in part 213. As proposed, part 213 would apply to the entity that initially produces a medical gas and also to any downstream firms that manufacture, process, pack, or hold medical gases, including firms that combine, commingle, refill, or distribute designated medical gases and medically appropriate combinations thereof. Part 213 is not intended to apply to entities further upstream in the supply chain from the entity that initially produces a medical gas. FDA seeks comment on the scope of these requirements, including the stage of product development at which they would apply and the entities that would be subject to the requirements. In this section, FDA will first describe proposed revisions to parts 210 and 211. Then FDA will describe the proposed requirements in part 213, including how they would differ from the requirements in part 211. Lastly, FDA will describe certain groups of CGMP requirements under part 211 that FDA is not proposing in part 213.

1. Proposed Revisions to Parts 210 and 211

FDA proposes conforming edits to parts 210 and 211 to account for the proposed new part 213. In part 210, FDA proposes to add references to part 213 in § 210.1(a) and (b) and in § 210.2(a) and (b) so that applicable provisions in part 210 would reflect the new CGMP regulations for medical gases in part 213.

In § 211.1(a), FDA proposes to add “medical gases as defined in § 213.3(b)(12)” to the parenthetical that currently excludes positron emission tomography drugs from part 211.

Proposed part 213 would contain the CGMP requirements for medical gases.

FDA also proposes to delete § 211.94(e). Instead, proposed § 213.94 would contain updated requirements for medical gas containers and closures that are generally consistent with the current requirements in § 211.94(e), with some additional provisions. More information is in section V.B.6 of this document.

FDA proposes to delete the last sentence of § 211.125(c), which waives labeling reconciliation requirements for 360° wraparound labels on portable cryogenic medical gas

containers because labeling reconciliation for medical gases would be addressed by proposed § 213.125(b).

FDA proposes to delete the reference to “containers of compressed medical oxygen” in § 211.132(c)(1), which is in a parenthetical that excludes certain products from the requirement for each retail package of an over-the-counter drug product covered by § 211.132 to bear a particular statement regarding its tamper-evident features. This reference would no longer be relevant if this proposed rule is finalized because medical gases (including compressed medical oxygen) would no longer be subject to part 211.

FDA proposes to delete the statement in § 211.170(b) that reserve samples of compressed medical gases need not be retained. Under the proposed rule, medical gases would be subject to proposed part 213, which would not include reserve sample requirements.

FDA proposes to delete the exception in § 211.196 that distribution records for compressed medical gas products are not required to contain lot or control numbers because distribution records requirements for medical gases would be addressed by proposed § 213.196.

2. General Provisions

Section 213.1 explains the scope of FDA’s proposed CGMP requirements for medical gases. Proposed part 213 would contain the minimum CGMP requirements for preparation of all medical gases for administration to humans or animals, including designated medical gases, medically appropriate combinations of designated medical gases, medical gases that are approved under an application that was submitted to FDA under section 505 or 512 of the FD&C Act, and any marketed unapproved drugs that are medical gases. Because designated medical gases and other kinds of medical gases share many of the same physical characteristics and are manufactured, processed, packed, and held using similar operations and control strategies, FDA believes that continuing to have a single set of CGMP requirements for all medical gases is appropriate.

FDA does not consider the process of mixing or combining gases by a hospital or healthcare provider at the point of care and as part of the ordinary practice of treating individual patients to be activities subject to part 213.

Part 213 applies to all designated medical gases and medically appropriate combinations thereof, regardless of whether they are intended for use in humans, animals, or both.

Proposed § 213.3 includes several definitions that generally track those in part 210, some of which have been revised to tailor them more specifically to medical gases. Proposed § 213.3 also contains new definitions that are relevant to the manufacture, processing, packing, and holding of medical gases. Proposed paragraph (a) would generally apply the definitions and interpretations in section 201 of the FD&C Act to such terms when used in proposed part 213.

Proposed paragraph (b) contains additional definitions as follows:

- The term “acceptance criteria” is proposed to be defined in § 213.3(b)(1) to mean the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units). This is identical to the definition of the same term in part 210. The Agency believes that establishing clear product specifications and acceptance/rejection criteria for determining whether a lot or batch is acceptable will help ensure the identity, strength, quality, and purity of medical gases.
- Proposed § 213.3(b)(2) would define the term “batch” to mean “a specific quantity of a medical gas or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.” This is generally consistent with the definition of the same term in part 210. The Agency believes this definition would allow for significant flexibility in defining a batch to address considerations raised by different types of firms and different manufacturing, processing, packing, and holding activities.

- The term “commingling or commingled” is proposed to be defined in § 213.3(b)(3) to refer to the act of combining one lot of designated medical gas or component with another lot or lots of the same designated medical gas or component. This is primarily intended to reflect the industry practice of combining designated medical gases of the same identity (e.g., nitrogen and nitrogen) from multiple original manufacturers or lots, all of which meet compendial standards. This definition would be new in part 213.
- In proposed § 213.3(b)(4), the term “component” is revised. Compared to the definition in § 210.3(b)(2) it means any ingredient intended for use in the manufacture of a medical gas, including those that may not appear in such gas. The term does not include incoming designated medical gases. Different proposed requirements in part 213 would apply to components and incoming designated medical gases. These proposed requirements are described further in section V.B.6 of this proposed rule.
- Proposed § 213.3(b)(5) defines the term “designated medical gas.” This definition refers to the statutory definition found in section 575(1) of the FD&C Act and is intended to apply to the gases described in section 575(1) of the FD&C Act.
- FDA also proposes to add a definition of the term “FDA” in § 213.3(b)(6) to mean the Food and Drug Administration. This is consistent with other Agency regulations that contain a definition of FDA.
- Proposed § 213.3(b)(7) defines the term “in-process material” to mean “any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the medical gas.” This is generally consistent with the definition of the same term in part 210.
- FDA proposes in § 213.3(b)(8) to define “incoming designated medical gas” to mean a designated medical gas received from one source that is commingled with the same gas from another source, used in a medically appropriate combination of designated medical gases or in the production of another medical gas, or further distributed. This definition is

intended to cover designated medical gases that downstream entities receive from original manufacturers and other sources. However, incoming gases that are not designated medical gases but that are intended for use in the manufacture of a medical gas would be considered components. As described above, FDA proposes different requirements for components and incoming designated medical gases. This definition would be new in part 213.

- In proposed § 213.3(b)(9), the term “lot” is defined to mean a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits. In the case of a medical gas produced by continuous process, the term means a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits. This is generally consistent with the definition of the same term in part 210.
- FDA proposes to define “lot number, control number, or batch number” in § 213.3(b)(10) to mean “any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of medical gas or other material can be determined” (§ 213.3(b)(11)). This is generally consistent with the definition of the same term in part 210.
- In proposed § 213.3(b)(11), the term “manufacture, processing, packing, or holding” is defined to include packaging and labeling operations, testing, and quality control of medical gases. This is generally consistent with the definition of the same term in part 210 because many provisions refer to these actions, and FDA intends that they have the same meaning as in part 210. FDA considers packaging in the context of these proposed requirements to include filling a container with a medical gas.
- FDA proposes in § 213.3(b)(12) that the term “medical gas” has the meaning given the term in section 575(2) of the FD&C Act. This would include designated medical gases,

medically appropriate combinations of designated medical gases, medical gases that are approved under an application that was submitted to FDA under section 505 or 512 of the FD&C Act, and any marketed unapproved drugs that are medical gases. This term would not include gases that are used as excipients in drug products that are not medical gases (e.g., propellants in inhalation drugs).

- FDA proposes to define “original manufacturer” in § 213.3(b)(13) to include persons or entities that initially produce a designated medical gas by chemical reaction, physical separation, compression of atmospheric air, purification of a gas, or other means. FDA’s intent is to capture the various methods by which firms produce designated medical gases. A person who refills a designated medical gas into a new container, either for further distribution or at the delivery site, would not be considered an original manufacturer. Additionally, a person who creates a medically appropriate combination of designated medical gases would not be considered an original manufacturer. This proposed definition would be new in part 213.
- FDA’s proposed definition of “quality unit” in § 213.3(b)(14) is any person or persons designated with the authority and responsibility for overall quality management and other responsibilities as defined in § 213.22. Under proposed part 213, the quality unit’s responsibilities would include oversight of quality throughout the entire manufacturing process. We are proposing to use the term “quality unit” because the Agency believes this term more appropriately reflects current terminology. As FDA has previously noted, the Agency considers “quality control unit” (defined in § 210.3(b)(15)) and “quality unit” to be synonymous. FDA proposes an updated definition for part 213 that focuses on “overall quality management” rather than quality control. The Agency believes that this definition would better reflect industry practice and the Agency’s understanding of the responsibilities of the quality unit.

- FDA’s proposed definition of “strength” in § 213.3(b)(15) is generally consistent with the definition in part 210, and contains two parts: (1) the concentration of the medical gas (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or (2) the potency, that is, the therapeutic activity of the medical gas as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

FDA seeks comment on whether there are other terms, including those that are used in this proposed rule or in parts 210 and 211, that the Agency should define in part 213.

3. Organization and Personnel

Proposed § 213.22 describes the responsibilities of the quality unit and is similar in scope to § 211.22. Proposed paragraphs (a) through (d) are generally consistent with paragraphs (a) through (d) in § 211.22, with one notable change: FDA proposes to use the term “quality unit” instead of “quality control unit.” Paragraph (a) would require that there be a quality unit with the responsibility and authority to approve or reject all components, medical gas containers and closures, in-process materials, packaging material, labeling, and medical gases, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. Additionally, the quality unit would be responsible for approving or rejecting medical gases manufactured, processed, packed, or held under contract by another company. The Agency believes that assigning dedicated staff to these quality responsibilities is critical to ensuring the identity, strength, quality, and purity of the medical gas.

Paragraph (b) would require that there be made available to the quality unit adequate laboratory facilities for the testing and approval (or rejection) of components, medical gas containers and closures, packaging materials, in-process materials, and medical gases. The availability of such facilities would help the quality unit perform its functions.

Under paragraph (c), the quality unit would have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity

of the medical gas. The Agency believes this provision would provide clarity regarding these responsibilities and that the quality unit is best positioned to determine whether these procedures and specifications are appropriate.

Paragraph (d) would state that the responsibilities and procedures applicable to the quality unit shall be in writing and shall be followed. The Agency believes this would help provide additional assurance for reliable continuation of established policies and procedures regarding product quality.

Paragraph (e) would clarify that quality unit personnel may perform other functions if there are appropriate written controls in place to ensure such other functions are performed separately from quality unit responsibilities and such other functions do not interfere with the quality unit's responsibilities or subordinate the quality unit's responsibilities to any other unit. Small firms that manufacture, process, pack, or hold a drug, including medical gases, have limited personnel who may have multiple roles within the firm. So long as there are appropriate written controls in place to ensure that other functions do not interfere with the quality unit's responsibilities or subordinate the quality unit's responsibilities to any other unit, FDA considers it acceptable for quality unit personnel to perform these other functions.

Proposed § 213.25 addresses personnel qualifications and responsibilities. Paragraph (a) would contain requirements for personnel education, training, and experience that are generally consistent with those contained in § 211.25, except as described below. Under proposed § 213.25(a), persons engaged in the manufacture, processing, packing, or holding of a medical gas would be required to have the education, training, and experience (or any combination thereof) to enable them to perform assigned functions. Training would have to be in the employee's particular operations and in CGMP (including in the applicable CGMP regulations and written procedures required thereunder). Training in CGMP would have to be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them. FDA proposes to specify in §

213.25(a) that written documentation must be maintained demonstrating employees' completion of training, including the date, type of training, and results of any completion criteria, such as test results. The Agency believes that these requirements would be sufficient to allow firms to maintain properly trained staff capable of accomplishing all required tasks. This paragraph would apply to all personnel engaged in the manufacture, processing, packing, or holding of a medical gas, including supervisors and subordinates. Therefore, we are not proposing a separate requirement similar to § 211.25(b) regarding supervisor responsibilities in this proposed rule.

Paragraph (b) would require that there be an adequate number of qualified personnel to perform manufacturing, processing, packing, and holding activities for each medical gas. The scope of this proposed requirement is the same as in § 211.25(c). This proposed requirement is important to ensure that all steps related to manufacturing, processing, packing, and holding are performed or monitored appropriately. What would constitute "adequate" personnel would depend in part on the size and complexity of the operations being performed.

Paragraph (c) would restrict access to "limited-access areas" to authorized personnel only. This proposed requirement is the same as § 211.28(c) and is important for medical gases because of the danger associated with mishandling medical gases and the risks to patients if such gases are improperly manufactured.

In § 213.34, FDA proposes requirements regarding consultants that are generally consistent with requirements that currently apply to medical gases under § 211.34. FDA does not see a need for different training and experience requirements for consultants advising on medical gases compared to other drug products. Consultants would be required to have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Further, records would be required to be maintained that state the name, address, and qualifications of any consultants and the type of service they provide.

4. Buildings and Facilities

FDA proposes a more limited set of building and facilities requirements for the manufacture, processing, packing, or holding of medical gases compared to part 211. FDA's primary concern regarding buildings and facilities used for these products is the risk of mix-ups because multiple gases are often produced at these buildings and facilities, and a gas mix-up could lead to patient harm. Additionally, while the risk of contamination is diminished for medical gases because they are generally manufactured in a closed, sealed system, periodic cleaning and maintenance is necessary for all buildings and facilities, so buildings and facilities must be designed to facilitate such cleaning and maintenance. The proposed requirements in this subpart are intended to address these risks, taking into account the unique manufacturing processes for medical gases.

Proposed § 213.42(a) would require that buildings and facilities used in the manufacture, processing, packing, or holding of a medical gas be of adequate design, including adequate space, for the orderly placement of equipment and materials to prevent mix-ups and allow for adequate cleaning, maintenance, and proper operations. Specifically, buildings and facilities would be required to be of adequate design to prevent mix-ups between components, incoming designated medical gases, medical gas containers and closures, labeling, in-process materials, or medical gases. FDA proposes to specify "buildings and facilities" in this section and elsewhere because some medical gas operations, including storage, can be performed outdoors without affecting the safety, identity, strength, quality, and purity of the product. FDA expects that there will be multiple ways of achieving adequate design and adequate space for all manufacturing operations that prevent mix-ups and allow for necessary cleaning and maintenance. Multiple gases are often manufactured at the same facility, and a mix-up could result in a patient receiving the wrong gas, which could be fatal. Therefore, it is essential that buildings and facilities be designed to enable personnel to clearly identify which equipment and materials are being used for which gas, to avoid such mix-ups. Moreover, while contaminants such as ordinary dust and

dirt are unlikely to enter a closed system, such contamination can still occur, for example, at the point at which a gas is transferred from one container to another.

Proposed § 213.42(b) would require that operations be performed within specifically defined areas of adequate size, with separated or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the following procedures:

- Receipt, identification, storage, and withholding from use of components or incoming designated medical gases, medical gas containers and closures, and labeling, pending the appropriate sampling, testing, or examination by the quality unit before release for manufacturing or packaging;
- Holding rejected components, incoming designated medical gases, medical gas containers and closures, and labeling before disposition;
- Storage of released components, incoming designated medical gases, medical gas containers and closures, and labeling;
- Storage of in-process materials;
- Manufacturing and processing operations;
- Packaging and labeling operations;
- Quarantine storage before release of medical gases;
- Storage of medical gases after release; and
- Control and laboratory operations.

Where multiple gases are being produced at the same facility, it is important for staff to be able to easily determine which gas is being manufactured in each area of the facility. These requirements will also help personnel distinguish between received, in-process, and finished product. FDA anticipates that firms can meet this requirement with physical barriers, signage, or both, though firms may use other appropriate means. Proposed § 213.42(b) would further require

that the flow of components, incoming designated medical gases, containers, closures, labeling, in-process materials, and medical gases be designed to prevent contamination and mix-ups.

Under proposed § 213.42(c), any building or facility used in the manufacture, processing, packing or holding of a medical gas shall be maintained in a clean condition so as to assure the safety, identity, strength, quality, and purity of the gas. Additionally, § 213.42(c) would require that written procedures applicable to the maintenance and cleaning of buildings and facilities be established and followed. FDA believes this proposed requirement is more limited than the sanitation requirement in § 211.56(a), and that it is better tailored to medical gas production, which involves a generally lower risk of contamination than other drug products. The condition of buildings and facilities that would be considered clean for medical gas production is expected to be different from the condition of buildings and facilities that would be considered clean for production of other drug products, where greater risks of contamination generally exist.

5. Equipment

Subpart D contains proposed requirements for equipment. Proposed § 213.63 would require that equipment be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. FDA expects that the design of the facility and equipment will allow for appropriate cleaning and maintenance (for example, personnel can access all equipment that must be cleaned). FDA expects that firms will ensure that pigtailed, valves, hoses, and similar connectors are kept clean and maintained.

Proposed § 213.65 addresses equipment construction and is similar to § 211.65. Paragraph (a) would require that equipment be constructed so that surfaces that contact components, in-process materials, or medical gases are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements. Paragraph (b) would require that substances required for operations, such as lubricants or coolants, shall not come into contact with components, containers, closures, in-process materials, or medical gases so as to alter the safety, identity,

strength, quality or purity of the medical gas beyond the official or other established requirements.

FDA proposes equipment maintenance and cleaning requirements under § 213.67. These proposed requirements differ from those that currently apply to medical gases under § 211.67 and reflect the differences in appropriate practices for routine cleaning of equipment associated with the manufacturing, processing, packing, and holding of medical gases. Paragraph (a) would require that written procedures be established, maintained, and followed for adequate cleaning and maintenance of equipment. Procedures would be required to include the following:

- assignment of responsibility for cleaning and maintaining equipment;
- maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
- a sufficiently detailed description of the methods, equipment, and materials used in cleaning and maintenance, as well as the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
- removal or obliteration of previous batch identification;
- protection of clean equipment from contamination prior to use; and
- inspection of equipment for cleanliness immediately before use.

FDA anticipates that these procedures would address, among other things: cleaning, or verifying as clean, equipment and product contact surfaces prior to initial use, after potential exposure to a contaminant, or as part of maintenance if such maintenance may expose the product contact surfaces to potential contamination; maintaining equipment at appropriate intervals to prevent malfunctions or contamination; and inspecting or testing systems prior to returning to service, to assure that no residual cleaning agents are present.

Proposed paragraph (b) specifies that such procedures shall not alter the safety, identity, strength, quality, or purity of the medical gas beyond established requirements.

Paragraph (c) would require that records be kept of cleaning, maintenance, and inspection as specified in § 213.180.

Proposed § 213.68 addresses requirements for automatic, mechanical, and electronic equipment used in the manufacture of medical gases. Paragraph (a) would require that such automatic, mechanical, and electronic equipment be routinely calibrated, inspected, and checked, according to a written program designed to ensure proper performance, and that written procedures and records of calibration, inspections, and checks be maintained. Ensuring that automated, mechanical, and electronic equipment is properly functioning is critical to ensuring the safety, strength, identity, quality, and purity of a gas. Without such checks, firms could manufacture gases that fail to meet compendial standards, or that are not appropriate for the ultimate patients' needs.

Paragraph (b) would require validation of computerized systems that record, store, or use data. The validation necessary would depend on how the computerized system is used in the manufacturing process.

In paragraph (c), FDA would require the maintenance of backup files of data entered into computer systems, though such backups would not be required where certain data, such as calculations, are eliminated by computerization or other automated processes.

Paragraph (d) would require that appropriate change control be used whenever modifications are made to computerized systems to assure that any changes do not adversely affect data integrity or product quality. FDA expects that this will include that manufacturers evaluate proposed changes with affected departments, that the proposed changes are assessed for revalidation where appropriate, and that activities are documented. Records would also be required to be maintained of such modifications.

6. Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures

Subpart E contains proposed requirements for control of incoming designated medical gases, components, and medical gas containers and closures. Proposed § 213.80(a) and (b) are similar to paragraphs (a) and (b) of § 211.80, though the proposed requirements would also apply

expressly to incoming designated medical gases. Paragraph (a) would require sufficiently detailed written procedures to be developed and followed describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, incoming designated medical gases, and medical gas containers and closures. Paragraph (b) would require that components, incoming designated medical gases, and medical gas containers and closures be handled and stored in a manner to prevent contamination and mix-ups. As previously mentioned, medical gases are generally manufactured in a closed, pressurized system, and gas mix-ups generally pose a more significant risk than contamination, considering previous incidents in which patients were administered the wrong gas (Ref. 8). However, while contamination poses a lower risk, there still exists the possibility for contamination. FDA believes that different controls would likely be appropriate for medical gas manufacturers to prevent contamination than would be expected for producers of other drugs.

Proposed paragraph (c) would require that lots of incoming designated medical gases or components be assigned a unique identification number, regardless of whether the incoming lot is used directly as supply or commingled with an existing supply. This would help facilitate the tracing of product once it enters distribution.

FDA is not proposing that part 213 include the requirements described in paragraphs (c) and (d) in § 211.80. FDA believes it is unnecessary to include the requirement in § 211.80(c) that product be stored off the floor and suitably spaced to permit cleaning and inspection. Sealed medical gas containers are designed to protect gases from contamination and external conditions, and their size and weight make storage off the floor impracticable in many settings. FDA also is not proposing to include in part 213 the requirement in § 211.80(d) that each container or grouping of containers for components or drug product containers, or closures be identified with a distinctive code for each lot in each shipment received. Gas containers are reused, and inspection of containers prior to reuse would be required under proposed § 213.84(a). Thus,

FDA believes that other lot identification requirements in proposed part 213 are sufficient to track product.

Proposed § 213.82 addresses the receipt and storage of incoming designated medical gases. The proposed requirements differ from currently applicable requirements in § 211.82 to better reflect the use of incoming designated medical gases in further manufacturing. Under proposed paragraph (a), a firm would have to verify and record upon receipt of a designated medical gas that the shipment contains a signed certificate of analysis (COA) from the supplier, and that the COA contains the following:

- the supplier's name;
- the name of the incoming designated medical gas;
- the lot number or another unique identification number;
- the actual analytical result obtained for strength, as well as the results of other tests performed (FDA expects these tests would include tests sufficient to demonstrate conformance with compendial standards);
- identification of the test method(s) used for analysis;
- the NDA and/or NADA number of the incoming designated medical gas; and
- the supplier representative's signature and the date of signature.

If the incoming designated medical gas is obtained from a supplier other than the original manufacturer, the shipment would also have to include complete information from the original manufacturer's COA. The firm would also be required to establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures. This is essential to ensuring that the information in the COA is accurate, and thus that the incoming designated medical gas meets relevant standards.

Proposed paragraph (b) would require that an identity test be conducted on incoming designated medical gases upon receipt. FDA understands that this is consistent with current industry practice (Ref. 2), and because designated medical gas manufacturers supplying the gas

will conduct full compendial testing, and the firm receiving the incoming designated medical gas would conduct full compendial testing prior to release (see proposed § 213.165), FDA believes this is an appropriate level of review.

FDA proposes § 213.84 regarding testing and approval or rejection of components, containers, and closures. Paragraph (a) would require that components, containers, and closures (including valves) be examined for conformance with appropriate written procedures and specifications, and approved or rejected, prior to the manufacturing or filling process. Firms can meet this proposed requirement by testing for conformance with written specifications. In lieu of such examination by the firm, a statement of verification that the component, container, or closure meets specifications may be accepted from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing provisions. This requirement would be satisfied with an auditing system. This type of evaluation system is intended to ensure the integrity of components, containers, and closures for the entire period of use. Rejected items would need to be handled in accordance with § 213.89.

Under proposed paragraph (b), firms would be required to take appropriate actions to protect against container and closure leaks. This would include performing leak tests on containers and closures at the time of fill and after fill but prior to release. FDA has evaluated inspectional findings from 2003 to 2021 and identified numerous instances of leaking or empty containers reported by customers and patients, following release by the manufacturer (Ref. 9). Because of the location and delayed timing of these defects, it appears some are likely not detectable prior to release. Therefore, additional controls may be needed to further protect against container and closure leaks to provide sufficient assurance of the durability of the container closure system throughout its period of use. For example, the inclusion of representative leak tests at additional intervals, such as upon pick-up or receipt of the container by the manufacturer, may be an additional adequate control. FDA seeks comment, with related

data and explanation, from manufacturers, distributors, and end users of medical gases and other interested parties on whether leak testing at the time of fill and after fill but prior to release would sufficiently ensure the integrity of the container closure system for the period of use, and whether additional periodic leak tests would enhance the ability to correct and prevent container closure defects that are only detectable after they leave the manufacturer.

Proposed paragraph (c) would require that components be sampled, tested, and approved or rejected as appropriate prior to use. Firms would be able to meet this proposed requirement by performing testing for conformance with written specifications or by an identity test on the component accompanied by an acceptable COA from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures. Components are not always used in the manufacture of designated medical gases, but when they are used, FDA believes these proposed requirements are reasonable.

Proposed § 213.89 is similar to the requirements in § 211.89 in that rejected components, containers, and closures would need to be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable, but proposed § 213.89 would also apply to incoming designated medical gases. Such a quarantine system need not include physical quarantining, as other methods can adequately ensure that unsuitable products are not used. FDA proposes to add a requirement that rejected components, incoming designated medical gases, and medical gas containers and closures be documented and assessed. This additional proposed requirement would help to ensure that any trends that warrant further investigation can be identified.

Proposed § 213.94 would contain additional requirements for medical gas containers and closures. Paragraph (a) is generally consistent with the requirements in § 211.94(a) and would require that containers and closures not be reactive, additive, or absorptive so as to alter the

safety, identity, strength, quality, or purity of the medical gas beyond the official or established requirements.

Under paragraph (b), container closure systems would be required to provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the medical gas. This is generally consistent with the requirements in § 211.94(b).

Paragraph (c) would require that medical gas containers and closures be clean to assure that they are suitable for their intended use. This is generally consistent with § 211.94(c), but FDA does not propose to include the requirements related to sterilization or removal of pyrogenic properties, as those are not relevant to medical gases.

Under proposed paragraph (d), standards or specifications, methods of testing, and, where indicated, methods of cleaning shall be written and followed for medical gas containers and closures. This is generally consistent with § 211.94(d), but FDA does not propose to include the requirements related to sterilization or removal of pyrogenic properties, as those are not relevant to medical gases.

Proposed paragraph (e) is a revised version of § 211.94(e) and would contain requirements for medical gas containers and closures. In paragraph (e)(1), FDA proposes that portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver-brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the container's use) except by the manufacturer. Proposed § 213.94(e)(1) is consistent with § 211.94(e)(1). Consistent with § 211.94(e)(1), FDA proposes to define "manufacturer" for purposes of § 213.94(e)(1) to include any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers. The Agency believes only such manufacturers should be able to remove or replace gas-specific use outlet connections that are attached to the valve body. Also, consistent with

§ 211.94(e)(1), FDA proposes to define “portable cryogenic medical gas container” for purposes of § 213.94(e)(1) as one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, healthcare entity, nursing home, other facility, or home healthcare setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term would not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655). The Agency believes all portable cryogenic medical gas containers should have gas-specific use outlet connections that are attached to the valve body in order to prevent gas mix-ups. FDA seeks comment regarding whether the scope of the exception to the term “portable cryogenic medical gas container” is appropriate, especially as the exception would include small cryogenic containers for use by individual patients.

Under paragraph (e)(2), FDA proposes to add the requirement that portable cryogenic medical gas containers as defined in proposed § 213.94(e)(1) as well as small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined in § 868.5655) have a working gauge sufficient to indicate whether the container has an adequate supply of medical gas for continued use. This is intended to enable end users, such as healthcare practitioners, patients, and caretakers, to monitor the gas remaining in the container. Without such a gauge, end users may not be able to determine when the container needs to be refilled or replaced. Additionally, if a container is stored for a long period of time before use and, during that time, slowly vents or leaks, the end user will be able to determine with a working gauge whether there is still gas in the container. FDA believes that the term “working gauge” would allow for flexibility, so that firms may use the type of gauge appropriate to measure the remaining volume or weight of medical gas, in liquid or gaseous form, as appropriate. FDA believes that the proposed requirement to have a working gauge would help to assure the safety,

identity, strength, quality, and purity of medical gases in portable cryogenic containers and small cryogenic containers for use by individual patients throughout their period of use.

Paragraph (e)(3) would contain the label and coloring requirements that currently apply to medical gases under § 211.94(e)(2), except that it would not include the requirement that the labeling not be susceptible to becoming worn or inadvertently detached during normal use. Because medical gas containers are reused and distributed among multiple entities, FDA believes that labeling inspection requirements proposed in this rulemaking would be sufficient to assure that labeling that enters into distribution is complete, accurate, durable, and readable, and that unsuitable labeling is replaced.

7. Production and Process Controls

Subpart F contains FDA's proposed requirements for production and process controls for medical gases. The proposed requirements in § 213.100(a) and (b) are generally consistent with the currently applicable requirements in § 211.100. Proposed paragraph (a) would require written procedures for production and process controls designed to assure that medical gases have the identity, strength, quality, and purity they purport or are represented to have. The procedures would need to include all requirements in subpart F. Further, the procedures, including any changes, would need to be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Paragraph (b) would require that written production and process control procedures be followed in the execution of the various production and process control functions and documented at the time of performance, and that deviations be recorded and justified. FDA believes that the existing requirements for developing and following written procedures for production and process controls are appropriate for medical gases because they would help ensure consistent compliance with a firm's established procedures for production of medical gases.

In § 213.101, FDA proposes different requirements for charge-in of components and incoming designated medical gases than those in § 211.101. Proposed paragraph (a) would

require that, except when a monograph or formulary specifies a range, the batch be formulated with the intent to provide 100 percent of the labeled or established amount of each medical gas. Where a monograph or formulary specifies a range for the contents of a medical gas, the medical gas would be required to be formulated with the intent to provide an amount within that specified range. Because medical gases are often manufactured continuously in a closed system, weighing, measuring, and subdividing components is generally not performed. Paragraph (b) would require that components and incoming designated medical gases added to in-process supply or final product containers be weighed or measured as appropriate. Final product and in-process supply containers would also be required to identify the name of the component or designated medical gas or the name and percentage of each component or designated medical gas if they contain multiple components or designated medical gases, as well as the unique lot number assigned.

Proposed § 213.110 would include a more limited set of sampling and testing requirements than the existing requirements in § 211.110, which contain several testing requirements that are inapplicable to medical gases (including tablet or capsule weight variation, disintegration time, and dissolution time and rate). Paragraph (a) would require that in-process materials be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality unit during the production process. Under paragraph (b), written procedures would be required to be established and followed describing the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures would need to be established to monitor the output and to validate the performance of those manufacturing processes. This is important for assuring batch uniformity and the integrity of drug products. Paragraph (c) would require that rejected in-process materials be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable. FDA believes that these proposed requirements would be sufficient to help ensure that medical gases are

manufactured according to specifications and prevent mix-ups or the accidental use of rejected or quarantined product.

8. Packaging and Labeling Control

Proposed subpart G would contain packaging and labeling control requirements. FDA proposes packaging and labeling materials examination and usage criteria in § 213.122. The proposed requirements in paragraphs (a) through (e) are generally consistent with the current requirements in paragraphs (a) through (e) in § 211.122. Paragraph (a) would require that there be sufficiently detailed written procedures describing the receipt, identification, storage, handling, sampling, examination and/or testing of labeling and packaging materials and that such procedures be followed. Further, paragraph (a) would require that labeling and packaging materials be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a medical gas. Paragraph (b) would state that labeling or packaging materials may be approved and released for use if they meet appropriate written specifications, and that they must be rejected if they do not meet such specifications to prevent their use in operations for which they are unsuitable. Paragraph (c) would require that records be maintained for each shipment of each different labeling and packaging material indicating receipt, examination, and whether the materials were accepted or rejected. Paragraph (d) would require that labels and other labeling materials for each different medical gas, strength, or quantity of contents be stored with suitable identification to avoid mix-ups. Further, access to storage would need to be limited to authorized personnel. Paragraph (e) would require the destruction of obsolete and outdated materials, as well as materials that do not meet applicable requirements.

Under paragraph (f), FDA would require one of three special control procedures for packaging and labeling operations: dedicated labeling and packaging lines for each strength of each medical gas; use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations; or use of visual inspection to conduct a 100 percent examination for correct labeling during or after

completion of labeling operations for hand-applied labeling (which would need to be performed by one person and independently verified by a second person). The Agency believes that utilizing one of these procedures is critical to preventing mix-ups. Paragraph (g) would require monitoring of printing devices on, or associated with, manufacturing lines used to imprint labeling upon the unit label or case to assure that all imprinting conforms to the print specified in the batch production record. Finally, paragraph (h) would allow the reuse of labels if they are legible, properly affixed to the container, and otherwise meet all applicable requirements. Unlike most drug containers, medical gas containers are reused many times and made of extremely durable materials. FDA believes that the proposed requirements in this section would be sufficient to ensure the quality and legibility of medical gas labels.

In proposed § 213.125, FDA would establish requirements for issuing labeling. Paragraph (a) would require that labeling and packaging operations be controlled to prevent labeling and product mix-ups, and that procedures be written and followed describing in sufficient detail the control procedures employed for the issuance of labeling. Proposed paragraph (b) would require use of procedures to reconcile the quantities of labeling issued, used, and returned, and would require evaluation of discrepancies found between the quantity of medical gas and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies would need to be investigated in accordance with proposed § 213.192.

Labeling reconciliation is proposed to be waived for cut or roll labeling if a 100 percent examination for correct labeling is performed in accordance with proposed § 213.122(f)(2) (100 percent electronic or electromechanical examination of labeling). Labeling reconciliation would also be waived for 360° wraparound labels on portable cryogenic medical gas containers. FDA is proposing to retain the label reconciliation requirement for medical gases except in the circumstances in which it would be waived, consistent with § 211.125, because label reuse may introduce risk into the labeling process that would not be present with unlabeled containers.

While reuse of cylinder labels and 100 percent verification of hand-applied labels on medical gas cylinders through visual inspection provides some assurance of correct labeling, such examination does not preclude the need for quality assurance steps, such as label reconciliation, to be built into the labeling process. The periodic replacement of cylinder labels that are worn, damaged or missing introduces variability and subjectivity into the determination of which and how many containers need new labels, potentially increasing the risk of mislabeling. The Agency considers label reconciliation procedures, designed commensurate with the risk, to be essential to the overall control of labels to minimize the potential for mix-ups.

Paragraph (c) would require that excess lot number stickers or decals bearing lot or control numbers be discarded. FDA expects that this will help prevent product mix-ups or the inclusion of incorrect lot information on a gas container. Finally, paragraph (d) would exempt bulk or transport containers (as defined in proposed § 201.161(c)(3)) from § 213.125. FDA believes that it is not necessary for this provision to apply to bulk or transport containers because end users are generally not expected to handle or use these containers to directly administer the gas to patients.

Proposed § 213.130 would require that written procedures be developed and followed to assure that the correct labels, labeling, and packaging materials are used for medical gases, similar to the requirements in § 211.130. These procedures would be required to incorporate the following features. Paragraph (a) would require physical or spatial separation from operations on other products. FDA expects this proposed requirement would help to prevent mix-ups. Additionally, FDA proposes to use the term “other products” because some firms that manufacture medical gases may also manufacture gases for non-medical purposes, such as for industrial use. Paragraph (b) would require that filled, unlabeled containers of medical gases that are set aside be identified and handled for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. It would not be necessary to apply identification directly to each individual container, but the firm would need to be able to identify the name,

strength, quantity of contents, and lot or control number of such containers. For example, this could be done through signage in the area in which the containers are stored.

FDA proposes in paragraph (c) that the medical gas be identified with a lot or control number that permits determination of the history of the manufacture and control of the batch. The lot or control number of the medical gas could be identified by use of a separate identification sticker or decal and would not need to be contiguous with other labeling information. Paragraph (d) would require, like the existing requirement in § 211.130(d), that packaging and labeling materials be examined for suitability and correctness before packaging operations, and that such examination be documented in the batch production record. FDA proposes to add a provision allowing product labels, including 360° wraparound labels, to be reused if they meet all applicable labeling requirements, all information on the label is legible, and the label is in good condition.

Paragraph (e) proposes the same requirements as those that currently apply under existing § 211.130(e). Under this proposal, firms would be required to inspect packaging and labeling facilities immediately before use to assure that all medical gases have been removed from previous operations. Moreover, this proposal would require inspection to assure that packaging and labeling materials unsuitable for subsequent operations have been removed, and the results of such inspection have been documented in the batch production records.

FDA proposes paragraph (f), which would exempt bulk or transport containers (as defined in proposed § 201.161(c)(3)) from the requirements of § 213.130, provided they are identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards. It is unnecessary for bulk and transport containers to bear the information required by this section because patients and healthcare providers are not expected to utilize them directly to administer a gas.

9. Holding and Distribution

Subpart H would establish holding and distribution requirements. Proposed § 213.150 would contain requirements for warehousing and distribution procedures. Paragraph (a) would require that written procedures be established and followed describing the distribution of medical gases. Such procedures would be required to include a system by which the distribution of each lot can be readily determined to facilitate any necessary recalls. FDA believes that the requirement in § 211.150(a) to distribute the oldest approved stock of a drug product first (often called the “first-in, first-out” requirement) is unnecessary to include in this proposed rule, as medical gases are generally not expected to expire or degrade under ordinary storage conditions. Paragraph (b) would require that written procedures be established and followed regarding warehousing of medical gases, similar to the requirements in § 211.142(a). These procedures would be required to include procedures for the quarantine of such gases before release by the quality unit. Unlike the current requirements in § 211.142(b), the proposed requirements would not include procedures regarding the conditions of drug storage because sealed, closed containers are generally expected to protect the gas inside from a wide range of environmental conditions. Moreover, the Agency believes the requirements in proposed §§ 213.42 and 213.80 would sufficiently address storage and handling.

10. Laboratory Controls

Subpart I proposes requirements for laboratory controls. In proposed § 213.160, FDA would incorporate the existing requirements in § 211.160, with one difference in § 213.160(b)(4). Proposed paragraph (a) would require that the establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by subpart I, including any changes, be drafted by the appropriate organizational unit and reviewed and approved by the quality unit. Such requirements would have to be followed and documented at the time of performance, and deviations recorded and justified.

Under proposed paragraph (b), laboratory controls would be required to include the establishment of scientifically sound and appropriate specifications, standards, sampling plans,

and test procedures designed to assure that components, medical gas containers, closures, in-process materials, labeling, and medical gases conform to appropriate standards of identity, strength, quality, and purity, and include the following four elements:

- Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, medical gas containers and closures, and labeling used in the manufacture, processing, packing, or holding of a medical gas. The specifications would be required to include a description of the sampling and testing procedures used. Samples would need to be representative and adequately identified. Such procedures would also need to require appropriate retesting of any component, medical gas container, or closure that is subject to deterioration. See § 213.160(b)(1).
- Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples would need to be representative and properly identified. See § 213.160(b)(2).
- Determination of conformance to written descriptions of sampling procedures and appropriate specifications for medical gases. Such samples would need to be representative and properly identified. See § 213.160(b)(3).
- The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met, or verification of such calibration. Instruments, apparatus, gauges, and recording devices not meeting established specifications would not be able to be used. See § 213.160(b)(4). This differs from § 211.160(b)(4) in that FDA proposes to require calibration or verification of calibration of instruments, apparatus, gauges, and recording devices. In the medical gas industry, some downstream entities may not conduct their own calibration. FDA believes

that verification of calibration is necessary if the entity does not conduct its own calibration.

Proposed § 213.165 would contain requirements for testing and release of medical gases for distribution. Paragraph (a) would require that there be appropriate laboratory determination of satisfactory conformance to final specifications for each batch, including the identity and strength, prior to release. The Agency omitted the requirements in § 211.165(b) from its proposal because generally there is less risk of microbial contamination for medical gases.

Section 213.165(b) would require that any sampling and testing plans be described in written procedures, and that such written procedures be followed. Such plans would need to include the method of sampling, the number of units per batch, and acceptance criteria. FDA believes it is unnecessary to incorporate in proposed § 213.165(b) the more detailed requirements regarding acceptance criteria described in § 211.165(d).

Proposed § 213.165(c) would require that the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm be validated and documented. This may be done in accordance with proposed § 213.194(a)(2). Further, the suitability of all testing methods would need to be verified under actual conditions of use.

FDA proposes § 213.165(d), which would require rejection of medical gases that fail to meet established standards or specifications and any other relevant quality criteria. This proposal is generally consistent with the requirements described in § 211.165(f), but FDA is not proposing to include the provision stating that reprocessing may be performed or the requirements for using reprocessed material. The Agency is not aware of reprocessing that occurs for medical gases. However, we welcome comment on this issue, including any example scenarios in which such gases are reprocessed.

Finally, FDA would clarify in § 213.165(e) that the proposed requirements in § 213.165 would not apply to the filling of a designated medical gas or medically appropriate combination via liquid to liquid into a container at a delivery site, often referred to by industry as “curbside

filling.” Because such filling operations are not expected to result in any material change in the gas being filled (for example, oxygen continues to be oxygen after filling), the gas is not expected to fall out of conformance with the requirements in § 213.165 if it is in conformance earlier in the distribution chain and stored under proper conditions.

FDA proposes in § 213.166 stability testing and expiration dating requirements for medical gases marketed under applications submitted under section 505 or 512 of the FD&C Act. Under proposed paragraph (a), any stability testing performed and any expiration date established for medical gases marketed under applications submitted under section 505 or 512 of the FD&C Act would need to be in accordance with the proposed requirements described in subsection (b), subject to the conditions established in their approved applications, if any. Under this proposed rule, stability testing and expiration dating would not be required for all medical gases. However, stability testing, expiration dating, or both would be required for some medical gases (for example, these would be necessary when required by an approved application for the safe and effective use of the drug, or stability testing would be necessary when an applicant chooses to label its product with an expiration date regardless of whether one is needed for safe and effective use under an approved application). FDA believes that this proposed requirement would allow for flexibility in determining whether stability testing, expiration dating, or both are necessary for a particular gas. Furthermore, specific stability testing requirements may vary depending on the particular gas.

Proposed paragraph (b) would contain requirements to assure that the medical gas meets applicable standards of identity, strength, quality, and purity at the time of use:

- The stability testing program would need to be designed to assess the stability characteristics of the medical gas and its container closure system. The results of stability testing would need to be used in determining appropriate storage conditions and any expiration dates included on the label. The stability program shall include the

appropriate sample size, test intervals, container closure systems, and storage conditions for samples retained for testing.

- Any expiration dates included on the label would be required to appear in accordance with § 201.17.
- Stability would need to be evaluated periodically to ensure that the medical gas continues to meet the standards for identity, strength, quality, and purity stated on the labeling to support the expiration date.

FDA is not proposing stability testing or expiration dating requirements for designated medical gases, as they are not expected to expire or degrade. Additionally, the proposed leak testing and working gauge requirements in this proposed rule are expected to address concerns regarding the container closure system's ability to prevent leakage. If a designated medical gas manufacturer chooses to include an expiration date on its container, FDA expects that such a date would be determined by appropriate stability testing that reflects the stability of the gas and the integrity of the container closure system.

11. Records

Proposed subpart J would contain requirements for records. Because FDA is not proposing to require the labeling of medical gases to bear expiration dates, except as proposed in § 213.166, the proposed requirements in § 213.180 differ from the requirements in § 211.180. Paragraph (a) would provide that all records that would be required under part 213, or copies of such records, be readily available for authorized inspection during the retention period and are subject to copying as part of such an inspection. The records would be able to be kept at either the establishment where the activities described in such records occurred or at another location from which the records can be immediately retrieved. Retrieval via computer or other electronic means would meet this requirement. Per paragraph (b), all records would have to be legible, stored to prevent deterioration or loss, and either original or accurate reproductions of original records. Paragraph (c) would require that all records that would be required to be maintained in

compliance with part 213 be maintained for at least 3 years from the date the batch of medical gas is distributed, except where otherwise provided. This timeframe is the same as that used in § 211.180(a) for over-the-counter drugs lacking expiration dating.

Paragraph (d) would require that written records required under part 213 be maintained so that their data can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures. Written procedures would also have to be established and followed for such evaluations. The procedures would also be required to include provisions for a review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch, and a review of complaints, recalls, returned or salvaged medical gases, and investigations conducted under § 213.192 for each gas. Under paragraph (e), firms would be required to develop written procedures for notifying responsible firm officials of any recalls, reports of inspectional observations by FDA, regulatory actions related to good manufacturing practice taken by FDA, or any investigations resulting from adverse event complaints.

Proposed § 213.182 would require that there be a written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use. These records would be required, as part of individual equipment logs, to show the date, time, product, and lot number of each batch processed. Individual equipment logs would not be required for equipment dedicated to one product, but lots or batches would have to follow in numerical order and be manufactured in numerical sequence in such a case. Also, where dedicated equipment is employed, the records of cleaning, maintenance, and use would be required to be part of the batch record. The individuals performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 213.68, just the person verifying such cleaning and maintenance) would have to date and sign or initial the log indicating the work was performed. Entries in the log would be required to be in chronological order. While FDA recognizes that cleaning of a closed,

pressurized system is not always appropriate, when it is applicable, it is essential to maintain adequate records of such cleaning.

FDA proposes in § 213.184 a more limited set of recordkeeping requirements for components, medical gas containers and closures, and labeling than those described in § 211.184. The records would include the results of any test or examination performed (including those performed pursuant to §§ 213.84 and 213.122) and the conclusions derived from the test or examination; documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 213.122 and 213.130; and the disposition of rejected components, containers, closures, and labeling. Medical gas containers are generally reused many times before they are taken out of service. FDA believes that the proposed requirements in §§ 213.84, 213.122, and 213.130 to evaluate containers and labeling are appropriate and sufficient to assure the quality of containers and the accuracy and legibility of their labels.

In § 213.186, FDA proposes master production and control recordkeeping requirements that are more tailored to medical gases than the current requirements in § 211.186. Paragraph (a) would require that master production and control records for each medical gas be prepared, dated, and signed to assure uniformity from batch to batch. Paragraph (a) would also require that the preparation of such records be described in a written procedure, and that such written procedure be followed. Paragraph (b) proposes to require certain information for each master production and control record. The records would be required to include: the product name and strength; a list of all components and any incoming designated medical gases used in manufacturing designated by names or codes sufficiently specific to indicate any special quality characteristics; a description of the containers, closures, and packaging materials and labels; and complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

These proposed requirements differ from the requirements in § 211.186 because of the differences in manufacturing and distribution of medical gases. For example, because medical gas manufacturing generally includes some venting of gas, measuring calculated excess of component, theoretical weight, and theoretical yield is infeasible.

In lieu of the requirements found in § 211.188, FDA proposes § 213.189, which would impose batch production and control recordkeeping requirements for each batch of medical gas produced. Paragraph (a) would require batch production and control records to be prepared for each batch of medical gas produced. Paragraph (b) would require that batch production and control records include documentation that each significant step in the manufacturing, processing, packing, and holding process was accomplished, including:

- Dates and times of each significant step, including in-process and laboratory tests as applicable. This documentation would include any prefill, filling, or post-filling inspections, which are essential to assuring product meets applicable standards.
- A description of the container for the medical gas, including the number and size of the containers filled as applicable. The containers used in manufacturing and filling operations can vary significantly, so documenting the containers is important for tracking purposes.
- Specific identification of each component and its source or in-process material used as applicable.
- Measures of components used in the course of processing as applicable.
- Testing results, including any in-process test results and finished product test results.
- Dated signature or initials of the persons performing and directly supervising or checking each significant event in the operation.
- Inspection of the packaging and labeling area before and after use.
- Complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate. Because labeling does not

always need to be applied due to the reuse of labels, documentation of these labeling control activities is important to help prevent mix-ups and the incorrect application of labeling.

- Any investigation made according to § 213.192.

Proposed § 213.192 would contain production record review requirements for medical gases. Under paragraph (a), manufacturing production and control records, including those for packaging and labeling, would need to be reviewed and approved by the quality unit to determine compliance with all established, approved written procedures before release or distribution of a batch. The quality unit would also be required to review production records to determine whether errors or unexplained discrepancies have occurred prior to batch release. If any errors or unexplained discrepancies have occurred, or a batch or any component of the batch fails to meet specifications, the firm would be required to conduct thorough investigations and take appropriate corrective actions. FDA further proposes to require a written record of the investigation, including the conclusions and followup. However, for entities that fill at a delivery site, paragraph (b) would require that production and control records be reviewed and approved by the quality unit to determine compliance with all established, approved written procedures within 1 business day after fill. FDA believes this additional time is needed for reviewing such records associated with filling at a delivery site because delivery personnel typically conduct such filling at multiple locations. As such, it is impractical for the quality unit to be present at the time of filling, and the characteristics of the gas are not expected to change during the filling process. Therefore, the Agency believes it is appropriate for the quality unit to review production and control records shortly after delivery is completed.

FDA recognizes that, because containers and labels are reused many times for medical gases, firms are generally unable to trace the history of a cylinder's use or identify the root cause of a cylinder-related problem. Nevertheless, if an error or unexplained discrepancy associated with a cylinder is identified, or if a cylinder is found not to meet any of its specifications, FDA

believes it is necessary for the firm to conduct a thorough investigation to identify the problem and take appropriate corrective action, such as taking a faulty cylinder out of circulation. FDA believes this proposal would establish production record review requirements that would assure that medical gases meet the requirements of the FD&C Act as to safety and have the identity, strength, quality, and purity they are purported or represented to possess.

FDA is also proposing § 213.194, which would impose laboratory recordkeeping requirements. Paragraph (a) would require that laboratory records related to the manufacture of a medical gas include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays. Laboratories would have to keep a complete record of all data created in the course of each test, including the records described in paragraphs (a)(1) through (4), as follows:

- A description of the sample, the batch or lot number to be tested, the date the sample was taken, and the date the sample was tested.
- The test method used, the test result, how the results compare with established standards of identity, strength, quality, and purity for the component, container, in-process materials (as applicable), and medical gas tested, a record of any calculations performed and any calculated results, and the unit of measurement of the result. It would not be necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction (for example $100 - 0.1 = 99.9$).
- Where applicable, any graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or medical gas for each lot tested.
- The initials or signature of the person performing the test as well as a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

Paragraph (b) would require that complete records be maintained of any modification of an established test method. These records would need to include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method. Paragraph (c) would require that complete records be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions. These requirements are the same as those that currently apply to medical gases under § 211.194(b) and (c).

Paragraph (d) would require that complete records be maintained of the periodic calibration or verification of calibration of laboratory instruments, apparatus, gauges, and recording devices that would be required by § 213.160(b)(4). This paragraph differs from § 211.194(d) in that it would allow for verification of calibration. It is FDA's understanding that it is common for some medical gas equipment to be calibrated by a supplier or other entity prior to arrival at the laboratory.

Paragraph (e) would require that complete records be maintained of all stability testing performed in accordance with proposed § 213.166. This requirement is consistent with the current requirement in § 211.194(e). As described above, only a subset of medical gases are expected to be subject to stability testing requirements, but for such gases, documentation of stability testing is essential to ensuring that the gas will maintain its stability for the expected timeframe.

Under proposed § 213.196, distribution records would be required to contain the name of the product, the lot or batch number, the consignee's contact information, and the date and quantity shipped. FDA believes that including the lot or batch number is essential to properly tracking and tracing product in the event a safety issue is discovered. Information about the dosage form, as required in § 211.196, is not necessary for medical gases because the dosage form is always "gas." For medical air and medically appropriate combinations of designated medical gases, the distribution record would also need to include the percentage of each gas.

FDA believes that this information is essential to prevent mix-ups because the concentration of each component would be clearly determined.

Proposed § 213.198 contains proposed requirements for complaint files that are similar to those requirements that currently apply to medical gases under § 211.198. Paragraph (a) would require that written procedures be established and followed for the receipt and handling of all written and oral complaints concerning a medical gas. These procedures would have to include a quality unit review of any complaint involving the possible failure of a medical gas to meet its specification as well as an investigation to determine the cause of the failure. An out-of-specification medical gas (for example, a combination containing higher quantities of oxygen than intended) could result in serious patient harm if administered. These procedures would also be required to include provisions for determining the need for an investigation under § 213.192 and determining whether the complaint represents an event that would need to be reported under proposed part 230.

Paragraph (b) would require that a written record of each complaint be maintained. This record would have to include the name of the medical gas, the lot or batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It would also be required to include the findings of any investigation and followup. If an investigation is not conducted, the record would need to include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Paragraph (c) would require the maintenance of complaint files in a manner such that they would be readily available for inspection by the firm or by FDA during an inspection. Complaint files would be required to be maintained for at least 1 year after the date that the complaint was received or for at least 3 years after distribution of the medical gas, whichever is longer. This proposed record retention period is the same as that used in § 211.180(a) for certain over-the-counter drugs lacking expiration dating and would facilitate review and evaluation by

the firm of information that is received after the event, thus facilitating the firm's ability to observe trends over time.

12. Returned and Salvaged Medical Gases

Subpart K contains proposed requirements for returned and salvaged medical gases. FDA proposes in § 213.204 to require that returned medical gases be identified as such and held. Moreover, if the conditions under which the returned gases have been held, stored, or shipped before or during their return, or if the condition of the gas, its container, carton, or labeling, as a result of storage or shipping, cast doubt on its safety, identity, strength, quality, or purity, the returned medical gas would need to be destroyed unless examination, testing, or other investigations prove the gas meets appropriate standards of safety, identity, strength, quality, or purity. These requirements would apply to situations in which a distributed medical gas is sent back to a firm due to a quality issue. Firms would need to maintain certain records of returned medical gases. Further, if the reason for a medical gas being returned implicates associated batches, an appropriate investigation pursuant to proposed § 213.192 would need to be conducted. Procedures for holding, testing, and use of returned medical gases would need to be in writing and followed. Proposed § 213.204 would not apply to the routine refilling of a cryogenic medical gas containers in the normal course of business unless the container was returned for a quality issue.

Proposed section 213.204 is largely the same as current § 211.204, with an added provision regarding routine refilling. FDA believes that the current requirements for returned drug product are appropriate for medical gases. However, the proposed routine refilling provision would be essential to address the fact that small amounts of gas are expected to remain in a returned container that will be reused. This situation is uncommon for other types of drug products, but medical gas containers are generally reusable, and complete purging of a container is impracticable. Another notable difference compared to § 211.204 is the omission of reprocessing requirements, as it is FDA's understanding that reprocessing of returned medical

gases does not occur. Generally, gases are reused if they meet specifications; otherwise, they are vented. FDA requests comment on this issue.

Section 213.208 would allow the salvaging of medical gases that have been subjected to improper storage conditions unless the gas's container has been subjected to adverse conditions that impact the identity, strength, quality, and purity of the medical gas, or the integrity of the container closure. These requirements would apply to situations in which a medical gas has been subject to improper storage conditions under the control of a firm responsible for the manufacture, processing, packing, or holding of the gas. Scenarios in which this may arise include natural disasters, facility structural damage (such as a building collapse), or exposure to smoke in the event of a fire. If there is a question whether the medical gas has been subjected to improper storage conditions, salvaging would only be permitted if there is evidence from laboratory tests that the gas meets all applicable standards of identity, strength, quality and purity, and the closure is not compromised. Section 213.208 also would require that firms maintain and follow written procedures for the holding, testing, and use of salvaged medical gases. While medical gases in sealed containers are generally considered unlikely to be affected by adverse conditions, such as natural disasters or significant changes in temperature, humidity, or pressure, a medical gas container could be damaged by such circumstances. Therefore, it is essential for firms to evaluate any containers potentially affected by adverse conditions.

13. Notable Part 211 Provisions FDA Does Not Propose To Include in Part 213

In this section, FDA discusses existing CGMP provisions of note that the Agency has not proposed for inclusion in part 213. In the proposed CGMP requirements described above in this section, FDA addressed some individual requirements in part 211 that the Agency has not proposed for inclusion in part 213, but this section addresses some other sets of requirements that are outside the scope of the above discussion. We specifically request public comment on these areas.

The requirements in § 211.28(a), (b), and (d) regarding personnel responsibilities are not included in this proposed rule. Medical gases are generally manufactured, stored, combined, and distributed under pressure in closed systems. Therefore, the risk of contamination is generally lower than for other drugs. FDA believes that the other requirements that would be established by this proposed rule would sufficiently address the risk of contamination in medical gases.

FDA is not proposing to include certain buildings and facilities requirements from part 211, subpart C, in proposed part 213, subpart C (specifically §§ 211.44 through 211.58) because they are not relevant to the manufacture, processing, packing, and holding of medical gases, or because the proposed requirements in § 213.42 sufficiently address these issues. For example, FDA believes that specific lighting requirements are not necessary because the risk of lightbulbs breaking and contaminating the gas inside a closed manufacturing system is remote. Moreover, FDA believes that the level of lighting at a facility would be sufficiently addressed by the requirements in § 213.42 to ensure that the design, space, and placement of equipment in a facility help protect against mix-ups (for example, we interpret this to mean that, among other things, employees have sufficient light to read labels). Similarly, specific ventilation requirements are not necessary because the closed manufacturing system for medical gases is generally unaffected by external factors such as air quality in the facility. Other specific requirements in part 211 regarding plumbing, sewage, and sanitation are also unnecessary because the risk of contamination is extremely low and because the proposed requirements in part 213 would adequately address these concerns.

The current requirements for filters in § 211.72 are also not included in this proposed rule. Because medical gases are not administered as injectable drugs, the requirements in § 211.72 are not relevant. FDA seeks comment on the need for filter requirements.

Because medical gases are generally not expected to expire or degrade under ordinary storage conditions, FDA does not believe it is necessary to include in this proposed rule the requirements in § 211.86 regarding using the oldest approved stock first or § 211.87 regarding

retesting product that has been stored for long periods of time or whose containers have been exposed to air.

FDA is not proposing to include a calculation of yield requirement similar to § 211.103. Gas loss is expected during manufacturing and can be variable even under normal operating conditions. The requirements proposed in part 213 would be sufficient to determine that the medical gas in the container is the amount and type indicated by the label and required by the final product specifications. Therefore, such a requirement would not provide useful information to firms or FDA.

FDA is not proposing to include an equipment identification requirement similar to § 211.105. Because equipment used for medical gas manufacturing is expected to be specific to the gas being manufactured, there is typically no changeover of machinery for firms to track. Accordingly, FDA does not believe such a requirement is necessary to assure the safety, identity, strength, quality, and purity of medical gases.

FDA is not proposing to include time limitations on production similar to § 211.111 because medical gases are generally not expected to expire or degrade under ordinary storage conditions. FDA also is not proposing to include requirements regarding the control of microbiological contamination similar to § 211.113 because the risk of contamination is extremely low for these products.

FDA is not proposing to include a requirement similar to § 211.115, which establishes requirements for reprocessing. The Agency is not aware that reprocessing occurs for medical gases. Rather, it is FDA's understanding that gases not meeting specifications generally would be vented. However, as mentioned above, we welcome comment on this issue, including any example scenarios in which medical gases are reprocessed.

FDA is not proposing to include the drug product inspection requirements in § 211.134. Because cylinders are reused many times, FDA believes that the labeling inspection provisions in proposed § 213.122(f) would assure proper product labeling.

FDA is not proposing to include the reserve sampling requirements in § 211.170 because the requirements in § 211.170 are not appropriate for medical gases. The proposed sampling requirements elsewhere in part 213 would be sufficient to address sampling for in-process and finished medical gases.

14. Proposed Revisions to 21 CFR Part 4 CGMP Requirements

FDA recognizes that some medical gases are marketed as part of a combination product. For example, a medical gas may be marketed with a device constituent part (for example, a portable liquid oxygen unit or a pressure regulator). However, a gas cylinder with a simple on/off valve (i.e., without a pressure regulator) would generally not be considered a device. Combination products are subject to part 4, subpart A (21 CFR part 4, subpart A), which clarifies the application of CGMP regulations to combination products and provides a streamlined approach to demonstrate CGMP compliance for facilities that manufacture co-packaged or single-entity combination products.

FDA intends to amend part 4, subpart A to reflect the new requirements for medical gases under part 213 and clarify how to comply with part 4, as amended. FDA proposes to include in 21 CFR 4.2 a definition of the term “medical gas” consistent with the definition in proposed part 213, as well as a definition of “medical gas CGMPs” that refers to part 213.

FDA also proposes to revise § 4.3(a) (21 CFR 4.3(a)) to account for combination products that contain a medical gas. For such products, part 213 would apply rather than parts 210 and 211, as described in proposed new § 4.3(e).

FDA proposes to include in § 4.4(b) (21 CFR 4.4(b)) specific provisions for combination products that include a medical gas as a drug constituent part to enable use of a streamlined approach for designing and implementing a CGMP operating system that complies with CGMP requirements for medical gas-device combination products akin to the streamlined approaches available for other drug-device combination products. FDA believes that when a manufacturer of a medical gas-device combination product demonstrates that its CGMP operating system

complies with part 213 in full, the provisions from part 820 (21 CFR part 820), with which manufacturers must demonstrate compliance, should be the same as those currently listed in § 4.4(b)(1) because part 213 covers the same general areas as part 211, and FDA is not aware of device characteristics that would necessitate a different approach. If a medical gas-device combination product manufacturer demonstrates that its CGMP operating system complies with part 820 in full, FDA believes that the following proposed requirements from part 213 would be appropriate to ensure that critical aspects of medical gas production are addressed:

- Section 213.84. Testing and approval or rejection of components, containers, and closures.
- Section 213.94. Medical gas containers and closures.
- Section 213.122. Materials examination and usage criteria.
- Section 213.165. Testing and release for distribution.
- Section 213.166. Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or 512 of the FD&C Act.
- Section 213.204. Returned medical gases.
- Section 213.208. Salvaging of medical gases.

FDA proposes to make other conforming edits as needed, such as revising § 4.4(e) to include a reference to part 213, and to clarify (where appropriate) throughout part 4, subpart A the requirements for medical gases.

FDA specifically seeks comment on this proposal, including: (1) which part 213 provisions should be included in the list of provisions for combination products containing a medical gas as a drug constituent part for which the CGMP operating system has been shown to comply with part 820; (2) whether the part 820 provisions listed in § 4.4(b)(1) should be revised for combination products containing a medical gas as a drug constituent part to include other 820 requirements or to remove certain existing references to part 820 call-outs; and (3) whether it is appropriate to permit manufacturers to have the option of choosing to demonstrate compliance

with part 213 in full along with the part 820 call-out provisions or compliance with part 820 in full along with the part 213 call-out provisions.

The Agency believes that part 4, subpart A helps ensure appropriate implementation of CGMP requirements for combination products while avoiding unnecessary redundancy in CGMP operating systems for these products, and that, given the benefits of the approach in part 4, subpart A, it should include combination products that contain a medical gas. FDA expects that sponsors of medical gases submitted under section 505 of the FD&C Act with a delivery system are already aware that they are producing a combination product, and as such should already be familiar with the requirements in part 4, subpart A. For firms that combine a designated medical gas or medically appropriate combination of designated medical gases with a finished, off-the-shelf device, FDA expects that the burden for complying with the device CGMP requirements would be relatively low. In some cases, firms may be able to leverage information from their device supplier to demonstrate compliance with device call-outs. Additionally, some device provisions are not expected to apply in all cases; some class I devices are exempt from the design control requirements in 21 CFR 820.30, and the installation and servicing requirements in 21 CFR 820.170 and 820.200, respectively, are not applicable to all devices.

C. Proposed Certification and Annual Reporting Provisions

The proposed rule would establish, within new part 230, regulations setting forth the requirements for obtaining certification of a designated medical gas pursuant to section 576 of the FD&C Act. Since the passage of FDASIA, many applicants have sought marketing authorization for a designated medical gas under section 576 of the FD&C Act, and this proposed rule would codify that process in FDA's regulations while also providing additional clarity where necessary. As proposed, part 230 would contain the requirements for filing a certification request for a designated medical gas for human use, animal use, or both. FDA is also proposing to make certain provisions in parts 314 and 514 inapplicable to designated medical gases, given that part 230 would apply instead.

Sections 575 and 576 of the FD&C Act also authorize FDA to deem certain medical gases not listed in section 575(1)(A) through (G) to be designated medical gases (FD&C Act section 575(1)(H)) and to certify designated medical gases or medically appropriate combinations of such gases for certain indications for use not listed in section 576(a)(3)(A)(i)(I) through (VII) (FD&C Act section 576(a)(3)(A)(i)(VIII)). The Agency is not proposing regulations implementing these provisions as part of this rulemaking because the Agency does not expect to deem additional medical gases to be designated medical gases at this time. In addition, the Agency does not expect to certify designated medical gases for indications beyond those currently described in section 576 of the FD&C Act at this time. If, in the future, FDA decides it would be appropriate to deem additional medical gases to be designated medical gases or to certify designated medical gases or medically appropriate combinations of such gases for additional indications for use, FDA expects to undertake such actions without the need for further rulemaking.

FDA also notes that section 575(1)(F) of the FD&C Act provides that carbon monoxide is a designated medical gas if it “meets the standards set forth in an official compendium.” Section 201(j) of the FD&C Act defines “official compendium” to include the U.S. Pharmacopeia (USP), the official Homeopathic Pharmacopeia of the United States (HPUS), the official National Formulary (NF), or any supplement to any of them. There is currently no monograph in the USP or NF for carbon monoxide. There is a HPUS monograph for carbon monoxide, though it is inapplicable to carbon monoxide as a designated medical gas for use in lung diffusion testing. FDA does not intend to object to the marketing of carbon monoxide for use in lung diffusion testing as long as the product conforms to one of the alternatives in the Center for Drug Evaluation and Research’s Manual of Policies and Procedures 5310.7 Rev. 1, *Acceptability of Standards from Alternative Compendia (BP/EP/JP)* (Ref. 10). This proposed approach is consistent with the draft policy described in the draft guidance for industry entitled “Certification Process for Designated Medical Gases” (Ref. 1). If and when a monograph entitled “Carbon

Monoxide” is added to the USP or NF, FDA expects original manufacturers that wish to continue marketing carbon monoxide to promptly submit a certification request.

1. Definitions

Proposed § 230.3(b)(2) defines the term “applicant.” An applicant is proposed to be defined as any person or entity who submits a certification request for a designated medical gas under part 230, including supplements. This is generally the original manufacturer. An applicant would also include any person or entity who owns a granted certification for a designated medical gas under part 230. This definition is generally consistent with FDA’s use of the term “applicant” with regard to NDAs and ANDAs (see 21 CFR 314.3(b)), as well as NADAs and ANADAs (see 21 CFR 514.3).

FDA also proposes to define “certification request” as a submission under section 576 of the FD&C Act requesting certification of a medical gas as a designated medical gas. After a certification request is deemed to be granted, a designated medical gas is deemed, alone or in combination, as medically appropriate, with another designated medical gas or gases for which a certification or certifications have been granted, to have in effect an approved application under section 505 or 512 of the FD&C Act, subject to all applicable postapproval requirements, for the applicable indications for use described in section 576(a)(3)(A)(i)(I) through (VIII) of the FD&C Act.

FDA proposes to define “FDA or Agency” to mean the Food and Drug Administration, consistent with other Agency regulations.

2. General Requirements for All Certification Submission Types

Proposed § 230.50 would establish the general requirements related to designated medical gas certification requests. The requirements would apply to all submission types. Proposed § 230.50(a)(1) would provide that the certification process described in part 230, subpart B applies to designated medical gases for the indications described in section 576(a)(3)(A)(i) of the FD&C Act. Currently, manufacturers who intend to market medical gases that do not meet the

definition of designated medical gas, or who intend to market designated medical gases for indications not described in section 576(a)(3)(A)(i) of the FD&C Act, must obtain approval of that medical gas under part 314 or part 514, or both, as applicable. For example, if an applicant intends to market nitrous oxide for a use other than analgesia (see section 576(a)(3)(A)(i)(III) of the FD&C Act), the certification process in proposed part 230 would not be available for that drug product at this time. If FDA deems additional indications for use appropriate under section 576(a)(3)(A)(i)(VIII) of the FD&C Act, the certification process could extend to designated medical gases for those uses. However, as of the date of this proposed rule, FDA has not deemed any additional indications for use to be appropriate for any designated medical gases.

Also in § 230.50(a)(1), FDA proposes to require any person who seeks to initially introduce or deliver for introduction a designated medical gas into interstate commerce to file a request for certification. An applicant would be required to identify its intention to market their designated medical gas for human use, animal use, or both. If a certification is deemed to be granted, a designated medical gas, alone or in combination, as medically appropriate, with another designated medical gas or other designated medical gases for which a certification or certifications have been granted, would be deemed to have in effect, for the uses described in section 576(a)(3)(A)(i) of the FD&C Act:

- an approved application under section 505 of the FD&C Act, if the applicant requested certification solely for human use;
- an approved application under section 512 of the FD&C Act, if the applicant requested certification solely for animal use; or
- approved applications under sections 505 and 512 of the FD&C Act, if the applicant requested certification for both human and animal use.

(See section 576(a)(3)(A)(i); see also proposed § 230.105.) Applicants should submit one request per designated medical gas, regardless of how many of their facilities manufacture or will manufacture that designated medical gas. Persons who receive a designated medical gas

from an applicant or another person and fill the gas into containers, including via liquid to liquid at a delivery site, are not expected to submit certification requests under part 230 because the gas they are handling should be the subject of a granted certification held by another entity. (See also proposed § 213.82.)

Proposed § 230.50(a)(2) would describe the relationship between the proposed certification requirements in part 230 and parts 314 and 514. Proposed § 230.50(a)(2) would provide that any person that proposes to market a medical gas that is a new drug for human use must obtain approval under part 314, and any person that proposes to market a medical gas that is a new animal drug for animal use must obtain approval under part 514, unless the medical gas meets the definition of a designated medical gas, and the medical gas is proposed to be marketed, alone or in combination (as medically appropriate), with another designated medical gas or gases for which a certification or certifications have been granted, for a use described under section 576(a)(3)(A)(i) of the FD&C Act. “New drug” and “new animal drug” are defined in section 201(p) and (v) of the FD&C Act.

Proposed § 230.50(b) would outline the information that must be submitted in a certification request. In addition, though not a proposed requirement in this proposed rule, FDA recommends that the applicant include a cover letter describing the purpose of the submission (e.g., original certification, amendment to supply additional information requested by FDA). Such cover letters often provide context and information that would be helpful to the Agency as it processes certification requests. Under § 230.50(b)(1), the certification request would need to include the name, address, telephone number, and email address of the person or entity requesting certification. If the address of the entity requesting certification is not in the United States, the certification request would need to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States. Under § 230.50(b)(2), the certification request would also need to identify the type of submission as one of the following:

- Original certification request: an initial request for certification by an applicant for certification of a medical gas as a designated medical gas
- Amendment to a pending submission: a submission related to a pending submission that revises existing information or provides additional information, including responses to Information Request Letters
- Resubmission: a complete submission that has been revised and submitted again following a previous denial (if the applicant chooses to resubmit its submission, it would need to provide a written response to all deficiencies identified in FDA’s denial letter, along with other information required for certification requests; this would help assure that past deficiencies are addressed before applicants resubmit, thus promoting the efficient use of Agency resources)
- Supplement to a granted certification: any submission that contains a change to a certification that was previously granted
- Other: any submission that does not fit into one of the other categories described in this list

Under § 230.50(b)(3), the applicant would also need to include a description of the designated medical gas. Each designated medical gas certification request would need to include the name of the gas, as well as a certification statement that the designated medical gas meets the appropriate compendial standard. FDA intends to develop a designated medical gas certification form which would include a certification statement. The Agency anticipates the form would have OMB approval prior to the finalization of any proposed rule.

Under § 230.50(b)(4), applicants would also be required to include certain facility information in the certification request, including the name and address of the facility or facilities where the designated medical gas will be initially produced. FDA uses the term “facility” in this proposed provision to be consistent with the terminology in section 576(a)(1)(C) of the FD&C Act, which requires that a certification request include “[t]he name and address of the facility or

facilities where the medical gas is or will be manufactured.” For purposes of this proposed regulation, the term “facility” would be synonymous with the term “establishment” as it is used in part 207 (21 CFR part 207). Other facilities that only perform subsequent activities such as transfilling, mixing, or filling at a delivery site would not be considered “facilities” for purposes of this proposed regulation. Applicants would also need to include a brief description of the manufacturing or processing activities performed at each facility listed in the certification, which would include chemical reaction, physical separation, compression of atmospheric air, purification of a gas, or other activities to produce a designated medical gas. Applicants would also need to include an FDA Establishment Identifier (FEI), if one exists, and a Unique Facility Identifier (UFI) in accordance with the requirements of part 207 and section 510 of the FD&C Act (21 U.S.C. 360). If an applicant intends to open a new facility to manufacture the designated medical gas, FDA recognizes that the applicant may not have an FEI at the time of the certification request, as FEIs are generally assigned upon registration of a new establishment. However, for existing facilities, including the FEI in the certification request will assist FDA in monitoring its establishment inventory. Regarding the UFI, inclusion of this information will assist the Agency in linking certification requests to registration information required by section 510(b)(1) of the FD&C Act and 21 CFR 207.25(e). FDA’s preferred UFI is the Data Universal Numbering System (DUNS) number (Ref. 11). Firms can acquire a DUNS number at no cost. For amendments and supplements, only changes to the list of facilities would need to be submitted.

Under proposed § 230.50(b)(5), the applicant would be required to certify in its certification request that its methods, facilities, and controls used in manufacturing, processing, packing, and holding of the designated medical gas, as applicable, are adequate to ensure the gas’s safety, identity, strength, quality, and purity. This certification would be met by completing a field on the certification form referenced above. This information is critical to determining whether the medical gas manufactured at the facility is a designated medical gas

because it meets applicable compendial standards (FD&C Act section 576(a)(1)(D)). Designated medical gases generally have narrow compendial standards, and requiring an applicant to certify that it employs appropriate methods, facilities, and controls would help ensure consistent, quality manufacture of a gas that meets such standards.

Lastly, under § 230.50(b)(6), if the Agency deems any other information appropriate to determine whether the gas meets the definition of a designated medical gas, the applicant would be required to provide that additional information as well. This would generally be in the form of a written request by FDA for the additional information. The applicant may also provide other information that the applicant believes will assist the Secretary in evaluating the request.

Though FDA is not proposing changes to its registration and listing regulations as they apply to designated medical gases, FDA notes that firms must also comply with applicable registration and listing requirements in section 510 of the FD&C Act and part 207. For example, firms must register establishments and list designated medical gases, or update existing registration and listing information, pursuant to part 207, subparts B and D.

Proposed § 230.50(c) would describe the requirements for submitting a certification request. Applicants would be required to submit a signed, completed request for certification either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to the Center for Drug Evaluation and Research (CDER) Central Document Room. FDA encourages submission of certification requests through the NextGen Portal at <https://edm.fda.gov>. FDA intends to assign an NDA or NADA number (or both, if the applicant has expressed its intent to market the medical gas for human and animal use) for reference purposes when an original certification request is filed. If certification is granted, the applicant should use these application numbers in all further submissions to the Agency. If certification is not granted, and the applicant resubmits their certification request in the future, the previously assigned NDA and/or NADA number would continue to be the relevant application number(s).

Section 230.65 would allow applicants to withdraw a certification request that has not been deemed granted. An applicant could notify FDA that it withdraws its certification request at any time prior to the certification being deemed granted. Withdrawal of a certification request would not preclude refiling. If a certification request is withdrawn, FDA would retain the certification request, and if the applicant requests a copy via Freedom of Information Act (FOIA) request, FDA would provide it pursuant to the fee schedule in FDA's public information regulations.

3. Supplements and Other Changes to a Granted Certification

Section 230.70(a) of the proposed rule would require an applicant to submit a supplement if any information in the certification request has changed after the request has been deemed granted, including, but not limited to, the addition of a new facility manufacturing the designated medical gas, a change in contact information, or a change in the corporate name. FDA anticipates these are the most common types of information in the request that might change after certification has been deemed granted.

Under proposed § 230.70(b), the supplement would need to include a signed, completed request for certification form with the updated information in compliance with the requirements of § 230.50, and would need to be submitted no later than 30 calendar days after the date the change occurred. FDA proposes that supplements may be submitted after the fact because the Agency does not anticipate that the types of changes submitted in a supplement would need to be approved before the change occurs.

4. Change in Ownership of a Certification That Has Been Granted

Proposed § 230.72 would address situations in which a designated medical gas certification that has been granted undergoes a change in ownership, for example, due to a merger or acquisition. Proposed § 230.72 would expressly allow for the transfer of ownership of such a certification. When a transfer occurs, both the new and former owners would be required to submit certain information to FDA. Under proposed paragraph (a), the former owner would

be required to submit a letter or other document explaining that all rights to the certification have been transferred to the new owner. Under proposed paragraph (b), the new owner would be required to submit a supplement under § 230.70 signed by the new owner describing any changes in the conditions in the granted certification, and a letter or other document identifying the date the transfer of ownership is effective.

5. Annual Report

Proposed § 230.80(a) would require applicants to submit an annual report each year within 60 calendar days of the anniversary of the date the certification was deemed granted. Section 576(a)(2) of the FD&C Act provides that a certification request is deemed to be granted unless, within 60 days of its filing, FDA denies the request based on certain findings; FDA interprets the period of 60 days in this provision to mean a period of 60 calendar days. The applicant would be required to submit a signed, completed annual report form either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to CDER's Central Document Room. The annual report would be required to contain the following information from the prior 12 months, pursuant to proposed § 230.80(b):

- A summary of any significant new information that might affect the safety, effectiveness, or labeling of the designated medical gas. The applicant would also be required to include any actions it has taken or intends to take as a result of this information.
- The applicant would need to include the National Drug Code (NDC) numbers, the quantities distributed for domestic use, and the quantities distributed for foreign use. The disclosure of financial or pricing data would not be required.
- Any changes to the applicant's name or contact information. This information would need to be submitted in a supplement no later than 30 calendar days after the change occurred pursuant to proposed § 230.70, but the Agency believes that receiving all current information consolidated in an annual report will help FDA keep track of applicants and ensure that the Agency has current information.

- The applicant would need to include a list of current facilities, and a list of facilities that were used since the previous annual report (or since the certification was deemed granted) but are no longer in use.

This information would be critical to allow FDA to evaluate all changes to the product and its manufacturing since the most recent report and determine whether any changes have the potential to alter the identity of the gas such that it no longer meets the applicable compendial standard or the definition of a designated medical gas.

6. FDA Review of Certification Submissions

Under proposed § 230.100(a), as part of its review, FDA would consider information submitted with the certification submission along with any other available, relevant information of which FDA becomes aware. Such information could include information obtained from State or Federal officials, FDA inspection reports, or any other source. Per § 230.100(b), FDA proposes the following grounds for denying a submission:

- The medical gas that is the subject of the submission is not a designated medical gas. For example, FDA currently would deny a certification request for oxygen that fails to meet the standards for Oxygen, USP.
- The submission does not contain the required information or otherwise appears to lack sufficient information to determine that the medical gas is a designated medical gas. This may occur if the applicant fails to certify that the medical gas meets the applicable compendial standards, or if FDA obtains evidence that the medical gas fails to meet applicable compendial standards.
- The applicant's methods, facilities, and controls used for the manufacture, processing, and handling of the designated medical gas, as applicable, are not adequate to ensure its safety, identity, strength, quality, and purity, or
- Denying the request is otherwise necessary to protect the public health.

Under proposed § 230.100(c), within 60 calendar days of filing of a certification submission, FDA could contact the applicant to request additional information regarding the submission if it determines that the submission is missing required information, that FDA needs such information to determine whether the medical gas is a designated medical gas, or that FDA determines such information is necessary to protect the public health. This proposed provision would help applicants correct or complete their submission, or decide to withdraw, in a timely and efficient manner. Section 576(a)(2) of the FD&C Act provides that a certification request is deemed to be granted unless, within 60 days of its filing, FDA denies the request based on certain findings; FDA interprets the date of filing under this provision to mean the date that the certification request is received by the Agency. Upon receipt of an amendment to a pending certification request, this 60-day period would restart to allow FDA sufficient time to review new information received. FDA may find that the submission lacks sufficient information if, within the 60-day review period, FDA is unable to contact the applicant to obtain and evaluate the missing information or if FDA is able to contact the applicant but is not provided with the additional information within the 60-day review period.

Proposed § 230.100(d) would provide that, within 60 calendar days of filing of a submission, if FDA makes one of the findings described in proposed § 230.100(b), FDA will notify the applicant in writing that the submission is denied and provide the basis for FDA's determination.

7. When a Certification Submission is Deemed Granted

Proposed § 230.105 would provide that, unless FDA makes one of the findings described in § 230.100(b) and notifies the applicant within 60 calendar days of filing that the submission is denied, certification is deemed to be granted and the designated medical gas will be deemed to have in effect an approved application under section 505 or 512 of the FD&C Act, or both, for the indications specified in section 576(a)(3)(A)(i) of the FD&C Act. FDA would notify the applicant in writing and intends to post the letter on the Agency's website. The designated

medical gas for which a certification is deemed granted would be subject to all applicable postapproval requirements. If, however, FDA has not responded during the 60-day review time period, the applicant may begin marketing their designated medical gas unless and until FDA withdraws or revokes approval.

8. Withdrawal or Revocation of Approval of an Application for a Designated Medical Gas

Proposed § 230.150 describes requirements concerning withdrawal or revocation of approval of an application for a designated medical gas. Proposed paragraph (a) addresses withdrawal of approval. FDA proposes that it will notify the applicant and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in § 314.200 (21 CFR 314.200), § 514.200 (21 CFR 514.200), or both, as applicable, for any of the grounds listed in proposed paragraph (a)(1). FDA proposes that if the Secretary of the Department of Health and Human Services has suspended approval on a finding that there is an imminent hazard to public health, FDA will initiate the withdrawal process. Additionally, FDA proposes that it will initiate the withdrawal process if it makes any of the following findings:

- Clinical or other experience, tests, or other scientific data show that the designated medical gas is unsafe for use under the conditions of use upon the basis of which the application was approved;
- New evidence of clinical experience not available to FDA until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the designated medical gas is not shown to be safe for use under the conditions of use upon the basis of which the application was approved;
- Upon the basis of new information before FDA with respect to the designated medical gas, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-controlled

investigations as defined in 21 CFR 314.126, that the designated medical gas will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

- The application contains any untrue statement of a material fact.

In § 230.150(a)(2), FDA proposes that it may notify the applicant and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in § 314.200, § 514.200, or both, as applicable, if FDA makes any of the following findings:

- The applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports applicable to designated medical gases, including under sections 505(k) and 512(l) of the FD&C Act, part 230, and part 213, or that the applicant has refused to permit access to, or copying or verification of, its records;
- On the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the designated medical gas are inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Agency;
- On the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the labeling of the designated medical gas, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the Agency; or
- The applicant has failed to comply with the notice requirements of section 510(j)(2) of the FD&C Act (pertaining to the requirements regarding product listing updates).

Section 576(a)(4)(A) of the FD&C Act makes clear that the authority to withdraw or suspend approval under section 505(e) applies to designated medical gases that are deemed to have in effect approved applications under section 505 or 512. FDA believes the grounds proposed in § 230.150(a)(1) and (2) are consistent with the bases for withdrawing an application under section 505(e) of the FD&C Act.

Under proposed § 230.150(a)(3), FDA would also withdraw approval if the applicant requests its withdrawal because the designated medical gas subject to the application is no longer being marketed, provided none of the conditions listed in proposed paragraphs (a)(1) or (a)(2) applies. FDA proposes to consider such a written request for withdrawal to be a waiver of an opportunity for hearing otherwise provided for in this section. Such withdrawal, when requested by the applicant, would be without prejudice to refiling.

Under proposed paragraph (a)(4), FDA could notify an applicant that it believes a potential problem associated with a designated medical gas is sufficiently serious that the designated medical gas should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided under this section, to permit FDA to withdraw approval, and to remove voluntarily the product from the market. If the applicant agrees, FDA would not make a finding under paragraph (a), but would withdraw approval in a notice published in the *Federal Register* that contains a brief summary of FDA's and the applicant's views of the reasons for withdrawal.

Proposed paragraph (a)(5) provides that, if FDA withdraws an approval, the Agency will publish a notice in the *Federal Register* announcing the withdrawal of approval. This is consistent with the Agency's current practice to announce withdrawn approvals.

Under proposed paragraph (b), FDA could revoke the grant of a certification if FDA determines, after providing the applicant with notice and opportunity for an informal hearing in accordance with 21 CFR part 16, that the request for certification contains any material omission

or falsification. This is intended to implement section 576(a)(4)(B) of the FD&C Act. FDA proposes corresponding edits to 21 CFR 16.1(b)(2) to include reference to this provision.

9. Proposed Changes to Part 314

FDA proposes carving out designated medical gases from certain provisions in part 314 for which a corresponding provision specific to designated medical gases is proposed to be added to part 230. FDA also proposes carving out designated medical gases from certain provisions of part 314 that are not relevant to designated medical gases. Proposed new § 314.1(c) (21 CFR 314.1(c)) would list the provisions that FDA proposes no longer apply to designated medical gases.

A number of provisions in part 314 would continue to apply to designated medical gases.⁷ Section 314.80(g) (21 CFR 314.80(g)), regarding the electronic submission of safety reports, would continue to apply. FDA anticipates that the electronic format for submission of human drug individual case safety reports (ICSRs) will be the same as for other human drugs, and that existing guidance will be appropriate for human designated medical gas ICSRs.

The following provisions in § 314.81 (21 CFR 314.81) also would continue to apply:

- § 314.81(b)(3), which addresses submission of advertisements and promotional labeling, special reports upon written request from the Agency, notification of permanent discontinuance or an interruption in manufacturing, and the requirements for withdrawing an approved drug product from sale;
- § 314.81(c), which addresses submitting information related to multiple applications and patient identification requirements; and
- § 314.81(d), which authorizes FDA to withdraw approval of an application for failure to make reports required under § 314.81.

⁷ FDA has described its intention to issue a proposed rule that, among other things, would amend part 314 to modernize postmarketing safety reporting requirements for drugs (see RIN 0910-AI61 on Fall 2021 Unified Agenda of Regulatory and Deregulatory Actions), and FDA intends to update proposed § 314.1(c) to address any new or modified provisions added by that rulemaking that would not apply to designated medical gases.

FDA is not aware of any reason to exempt applicants from these requirements, though the Agency requests comment on the burden associated with complying with these provisions.

Subparts E and G of part 314 would also continue to apply. FDA has not identified any reason to establish different requirements and procedures for hearings, imports and exports, drug master files, or public disclosure of Agency records related to designated medical gases.

10. Proposed Changes to Part 514

Similarly, FDA proposes carving out designated medical gases from provisions in part 514 for which a provision specific to designated medical gases is proposed to be added to part 230. FDA also proposes carving out provisions that do not apply to certification requests for designated medical gases. Proposed revisions to § 514.1(a) list the provisions that FDA proposes no longer apply to designated medical gases. FDA proposes that the data confidentiality requirements, hearing procedures, and judicial review process would continue to apply because FDA has not identified any reason to establish different procedures for designated medical gases. Within § 514.80, FDA proposes revisions to the table and to paragraph (a) to further explain that NADAs for designated medical gases are not subject to the reporting requirements in § 514.80 and are instead subject to part 230.

D. Proposed Postmarketing Quality and Safety Reporting Provisions

Also within part 230, FDA proposes new postmarketing safety reporting requirements for designated medical gases.

1. Definitions

Proposed § 230.3(a) would incorporate relevant definitions from sections 201 and 575 of the FD&C Act. Additionally, FDA proposes several additional definitions in § 230.3(b) related to postmarketing safety reports along with the definitions described in section V.C. above. FDA proposes to define “adverse event” to mean any untoward medical occurrence associated with the use of a designated medical gas in humans or animals, whether or not it is considered related to the designated medical gas. This would include adverse events occurring in the course of the use

of a designated medical gas, adverse events occurring from overdose (whether accidental or intentional), adverse events occurring from abuse, adverse events occurring from discontinuation (such as physiological withdrawal), and any failure of expected pharmacological action.

The proposed definitions of “ICSR” and “ICSR attachments” would be generally consistent with the definitions of those terms in § 314.80(a). FDA proposes to define “ICSR” to mean a description of an adverse event related to an individual patient or subject. The Agency proposes to define “ICSR attachment” to mean documents related to the adverse event described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

FDA proposes to define “life-threatening adverse event” to mean any adverse event that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse event as it occurred. This term would not include an adverse event that, had it occurred in a more severe form, might have caused death.

The proposed definition of “minimum data set for an ICSR for an adverse event” is generally consistent with the list of minimum data elements for a postmarketing ICSR described in the 2001 draft guidance for industry “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines” (Postmarketing Safety Reporting Draft Guidance) (Ref. 12). FDA proposes that a minimum data set for an ICSR for an adverse event include the following four elements: (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect designated medical gas, and (4) an adverse event.

FDA proposes to define “nonapplicant” in a manner that is generally consistent with how the term is described in § 314.80(c)(1)(iii). A nonapplicant would be defined as anyone other than the applicant whose name appears on the label of a designated medical gas container as a manufacturer, packer, or distributor.

FDA proposes to include a definition of “serious adverse event.” Under this proposed definition, an adverse event would be considered serious if it results in: death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or

significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect. Important medical events that may not result in one of the above outcomes may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or study subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of product dependency or product abuse. Additional examples in animals include severe hypersensitivity reactions or respiratory distress.

2. Field Alert Reports

Section 230.205 contains the proposed requirements for field alert reporting for distributed designated medical gases and articles. Applicants would be required to submit a field alert report (FAR) to the FDA district office that is responsible for their facility concerning (a) information concerning any incident that causes the designated medical gas or its labeling to be mistaken for, or applied to, another article; and (b) information concerning any bacteriological contamination, or significant chemical, physical, or other change or deterioration in the designated medical gas, or failure of one or more distributed batches to meet established specifications. FARs would be required to be submitted within 3 working days of receipt by the applicant. FDA considers working days to be any day from Monday through Friday, excluding U.S. Federal holidays (Ref. 13). The Agency seeks comment on the appropriateness of the 3-day reporting period. FDA would accept receipt of a FAR by telephone or other rapid communication if the applicant promptly follows up in writing. Email is an appropriate method for rapid communication as well as followup. Proposed § 230.205 would also contain requirements for identifying a FAR submission.

Proposed § 230.205 is generally consistent with the FAR requirements in § 314.81(b)(1). FDA proposes to establish § 230.205 to clarify that designated medical gases for both human and

animal use would need to follow the same FAR requirements. FDA is not aware of any reason to establish different requirements for designated medical gases for animal use.

3. General Reporting Requirements for Designated Medical Gas Adverse Events

Proposed § 230.210 would contain general requirements for reporting adverse events related to designated medical gases.

Proposed § 230.210(a) would require applicants and nonapplicants to promptly review all safety information that the applicant or nonapplicant receives or otherwise obtains from any source (including both foreign and domestic sources). Examples of such sources would include safety information from commercial marketing experience, reports in the published scientific and medical literature, unpublished scientific papers, and reports from regulatory authorities (this would include domestic and foreign authorities).

As described below in sections V.D.4 and V.D.5, applicants and nonapplicants would be required to submit safety reports for designated medical gases pursuant to §§ 230.220 (for human use) and 230.230 (for animal use). Applicants and nonapplicants for a designated medical gas with both an approved NDA and an approved NADA would be subject to both the human reporting requirements in § 230.220 and the animal reporting requirements in § 230.230. However, both sets of reporting requirements would not apply at the same time for a given event. For example, if an adverse event associated with the use of a designated medical gas in a human patient occurs, the proposed requirements in § 230.220 would apply, but the proposed requirements in § 230.230 would not. Conversely, if an adverse event associated with the use of a designated medical gas in an animal patient occurs, the proposed requirements in § 230.230 would apply, but the proposed requirements in § 230.220 would not. In addition, if an adverse event occurs in a human from exposure during use of the gas in an animal patient, the proposed requirements in § 230.230 would apply, but those in § 230.220 would not. FDA considers an applicant responsible for information known to its employees, affiliates, and contractors. FDA

would similarly consider a nonapplicant responsible for information known to its employees, affiliates, and contractors.

Under proposed § 230.210(b)(1), reports or information submitted by applicants or nonapplicants (and any release by FDA of such reports or information) under § 230.220 or 230.230 would not necessarily reflect a conclusion that the report or information constitutes an admission that the designated medical gas caused or contributed to an adverse effect. Additionally, under proposed § 230.210(b)(2), applicants and nonapplicants would not need to admit, and they could deny, that the report or information submitted under § 230.220 or § 230.230 constitutes an admission that the designated medical gas caused or contributed to an adverse effect.

4. Human Designated Medical Gas ICSR Requirements

Proposed § 230.220 would contain requirements for submission of ICSRs associated with the use of a designated medical gas in humans. Under proposed § 230.220(a)(1), both applicants and nonapplicants would be required to submit each ICSR associated with the use of a designated medical gas in humans described in § 230.220(b) to FDA as soon as possible, but no later than 15 calendar days from the date when the applicant or nonapplicant has both met the reporting criteria in paragraph (b) and acquired a minimum data set for an ICSR for that adverse event.

The proposed timeframe for reporting adverse events under § 230.220(a)(1) is 15 calendar days. In contrast to § 314.80(c)(1)(iii), which describes circumstances under which a nonapplicant can elect to submit adverse drug experience reports to the applicant instead of FDA, FDA proposes in § 230.220 to require both applicants and nonapplicants to report adverse events involving designated medical gases directly to FDA. There are a large number of downstream entities that would meet the definition of “nonapplicant” and that combine, distribute, and fill designated medical gases, compared to a small number of upstream entities that would meet the definition of “applicant.” These downstream nonapplicants may receive

designated medical gases from multiple sources, including multiple applicants, and the gases may be commingled within a single tank. Therefore, FDA anticipates that it would be challenging for a downstream nonapplicant to trace the suspect gas to a specific upstream applicant if the nonapplicant becomes aware of a safety issue.

FDA also proposes that the 15-day period would be triggered upon the applicant both meeting the reporting criteria described in proposed § 230.220(b) and acquiring a minimum data set for an ICSR for an adverse event. This proposed requirement would help ensure that a minimum level of information is obtained prior to submission of the report so that the Agency has a more complete picture of the incident. Lastly, FDA is not proposing to include a requirement that an adverse event be unexpected to be subject to the proposed reporting requirement. Because designated medical gases are not required to be studied in clinical trials, which are commonly conducted for other drugs, to be certified under section 576 of the FD&C Act, designated medical gas applicants are not expected to generate the type of labeling information about expected adverse events that sponsors of other types of drugs typically generate during product development. Thus, we expect that the applicants and nonapplicants for designated medical gases that would have reporting obligations under this proposed rule would not be able to determine whether an adverse event was unexpected.

FDA is not proposing a requirement for periodic safety reporting for designated medical gases of the type required under § 314.80(c)(2). This would codify FDA's current approach with regard to the submission of periodic adverse drug experience reports as described in the March 2015 Compliance Program Guidance Manual 7356.002E, (Ref. 14). We do not believe it is necessary to incorporate such a requirement in the proposed postmarket safety reporting regulations that would apply to designated medical gases, but we welcome comment on this issue.

Proposed § 230.220(a)(2) would provide that applicants and nonapplicants should not resubmit ICSRs that they obtained from the FDA Adverse Event Reporting System database or

that FDA forwarded to them. This is generally consistent with § 314.80(b). FDA encourages applicants and nonapplicants not to resubmit such ICSRs. Duplicative reports can divert Agency resources away from other safety priorities and, if not identified as duplicates, may obscure signal identification.

Under proposed § 230.220(a)(3), applicants and nonapplicants would be required to submit to FDA new information they receive or otherwise obtain that is related to a previously-submitted ICSR or an ICSR that was sent to the applicant by FDA. Such information would need to be submitted within 15 calendar days after the applicant or nonapplicant receives or otherwise obtains the new information. If an applicant or nonapplicant receives or otherwise obtains new information related to a previously submitted ICSR, they would have to submit the information to FDA under this proposed rule. For example, if a physician submits information to an applicant about an adverse event related to the applicant's designated medical gas, the applicant submits an ICSR based on that information, and the physician updates the applicant in the future, any new information would need to be submitted to FDA as new information within 15 calendar days. This proposed requirement is important to ensure that FDA becomes aware of any new information that arises about the adverse event.

Proposed paragraph (b) would describe two types of ICSRs that must be submitted to FDA. First, applicants and nonapplicants would be required to report serious adverse events received. This would include ICSRs for serious adverse events reported to the applicant or nonapplicant spontaneously (such as reports initiated by patients, consumers, and healthcare professionals) as well as ICSRs for serious adverse events obtained from published scientific and medical journals either as case reports or as the result of a formal clinical trial. Unlike the safety reporting requirements in part 314, FDA is not proposing to include a requirement that the event be unexpected. Designated medical gases do not have traditional product labels that most human drugs and animal drugs bear, and their applicants generally have not conducted traditional

clinical trials that would typically generate robust adverse reaction information. Therefore, required serious adverse events must be submitted regardless of expectedness.

In proposed § 230.220(b)(1)(iii), FDA proposes to include one exception to the requirement that serious adverse events be reported within 15 calendar days. ICSRs would not be required for reports of a patient death in cases where the patient was administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the death was caused by the administration of oxygen. FDA recognizes that oxygen is commonly administered during end-of-life care or to patients with a life-threatening disease or who are otherwise in critical condition. Accordingly, FDA believes that unless there is evidence to suggest that the administration of oxygen caused a patient's death, such reports are unlikely to reflect an underlying safety signal.

Second, FDA proposes that, upon notification by FDA, an applicant would be required to submit, in a timeframe established by FDA, ICSRs for any adverse events that would not be required under proposed § 230.220(b)(1). FDA would specify the adverse events to be reported as well as the reason for requiring its reporting to the Agency. For example, FDA might take such action if it identifies a potential safety signal that would not otherwise be reported under § 230.220(b)(1), but the Agency needs additional information to fully evaluate the safety signal, including its seriousness and scope.

Under the proposed requirements in § 230.220, ICSRs would not need to be submitted for fires associated with oxygen use if the patient did not also experience a reportable adverse event. Applicants and nonapplicants who become aware of patients who experience a reportable adverse event associated with a fire related to oxygen use (such as burns or smoke inhalation) would be required to submit an ICSR. Because it is well-known that oxygen accelerates combustion and that smoking near an oxygen source can cause a fire, FDA believes it is unnecessary to receive reports in which the patient does not experience an adverse event.

Proposed paragraph (c) would describe the process for completing and submitting an ICSR. Under paragraph (c)(1), FDA proposes to require submission of ICSRs and ICSR attachments in electronic format that FDA can process, review, and archive, as described in § 314.80(g)(1). Should this proposed rule be finalized, FDA would incorporate designated medical gases into existing guidances on electronic submission of postmarketing safety reports under § 314.80(g)(1), as designated medical gases would be expected to use the same electronic reporting mechanism. Under § 230.220(c)(1)(ii), applicants and nonapplicants would be able to request in writing a temporary waiver of the requirements in § 230.220(c)(1)(i), as described in § 314.80(g)(2) (see also Ref. 15). Further, FDA would grant such waivers on a limited basis and for good cause shown.

Under proposed paragraph (c)(2), FDA proposes additional reporting requirements. Proposed paragraph (c)(2) would direct applicant and nonapplicants to submit each ICSR only once and would require applicants and nonapplicants to submit a separate ICSR for each patient who experiences an adverse event reportable under paragraph (b). FDA also proposes to require that adverse event terms described in an ICSR be coded using standardized medical terminology (e.g., the Medical Dictionary for Regulatory Activities). The use of standardized medical terminology facilitates sharing of regulatory information internationally for human medical products (Ref. 16). Additionally, the use of standardized medical terminology will facilitate electronic transmission of safety information in a format that FDA can process, review, and archive, as required under § 314.80(g)(1). ICSRs submitted under § 230.220 would be required to contain at least the minimum data set for an ICSR for an adverse event. The applicant or nonapplicant would need to actively seek the minimum data set in a manner consistent with proposed paragraph (f) and document and maintain records of their efforts. Inclusion of the minimum data set would similarly facilitate electronic transmission of safety information in the necessary format for FDA to process, review, and archive. Proposed paragraph (c)(2) would also require that the applicant or nonapplicant complete all known, available elements of an ICSR

described in proposed paragraph (d). For adverse events, applicants and nonapplicants would be required to actively seek any information needed to complete all applicable elements, consistent with the written procedures that would be required under proposed paragraph (f), and to document and maintain records of their efforts to obtain the missing information. However, if an adverse event is reportable under proposed § 230.220(b) but the ICSR is missing certain elements listed in paragraph (d) (i.e., elements other than the required minimum data set), FDA would still receive and review the ICSR. Lastly, proposed paragraph (c)(2) would require an applicant or nonapplicant to submit the following types of supporting documentation in an ICSR, if available:

- A copy of the autopsy report if the patient died, or a hospital discharge summary if the patient was hospitalized (to be submitted as an ICSR attachment in the manner specified); and
- A copy of the published article for each ICSR of an adverse event obtained from published scientific and medical literature (to be submitted as an ICSR attachment in the manner specified).

FDA seeks comment on the burden associated with complying with these proposed requirements. These proposed requirements also include required timeframes, translation of foreign language documents, and cross-referencing in the case of multiple ICSRs related to the same article.

Proposed paragraph (d) would describe the information to be included in an ICSR. This is generally the same list as in § 314.80(f), with a few exceptions. First, FDA is not proposing to require that the applicant or nonapplicant state whether the product is a combination product. Second, FDA does not propose to require the submission to include an expiration date because designated medical gases are not generally expected to have an expiration date under proposed part 213. Third, FDA does not propose to require the applicant or nonapplicant to state whether the product is a prescription or nonprescription product. With the exception of oxygen for

limited uses identified in section 576(b)(2)(A) of the FD&C Act, all designated medical gases are for prescription use, and the Agency expects that to continue to be the case. Fourth, FDA has proposed to combine the contact information in § 314.80(f)(5)(i) and (ii) into one bullet. Fifth, we propose to clarify in § 230.220(d)(5)(iv) that the applicant or nonapplicant would be required to submit the NDA and/or NADA number for their certification. Lastly, FDA proposes to require that the applicant or nonapplicant state whether the ICSR is an expedited report, rather than stating whether the ICSR is a 15-day alert report.

Proposed paragraph (e) would contain recordkeeping requirements. Applicants and nonapplicants would be required to maintain records of information related to adverse events under proposed § 230.220 for up to 10 years from the initial receipt of information. These records would need to be maintained regardless of whether the information was submitted to FDA. The records would also need to include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant. These proposed requirements are generally consistent with the requirements in § 314.80(j). FDA also proposes that, upon written notice, the applicant or nonapplicant would need to submit any or all of these records to FDA within 5 calendar days after receipt of the notice. Applicants and nonapplicants would also need to permit authorized FDA employees to access, copy, and verify these established and maintained records, at reasonable times. These proposed requirements will help facilitate the review of new and emergent safety issues, including of potential safety signals that may be associated with nonserious adverse events, which would not be required to be reported to FDA under proposed paragraph (b)(1).

Proposed paragraph (f) would require that applicants and nonapplicants develop written procedures to fulfill their obligations under proposed § 230.220 for the surveillance, receipt, evaluation, and reporting of adverse event information. This proposed requirement is generally consistent with existing requirements in § 314.80(b) and is appropriate for designated medical

gases. Additionally, we propose to specify that these procedures would need to address employee training and the obtaining and processing of adverse event information from other applicants and nonapplicants. Employee training is important to ensure that all personnel who may receive or handle adverse event information on the company's behalf fully understand their responsibilities. Processing adverse event information from other parties is also critical because of the many layers of distribution typical for designated medical gases.

Proposed paragraph (g) would contain proposed patient privacy provisions. Rather than including patient names and addresses in reports under proposed § 230.220, proposed paragraph (g) would recommend that applicants and nonapplicants assign a unique code to identify patients. Proposed paragraph (g) would recommend that applicants and nonapplicants include the name of the reporter from whom the information was received as part of the initial reporter information, even if the patient is the reporter. As set forth in FDA's public information regulations in part 20, FDA generally may not disclose the names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers submitted to FDA in adverse event reports. This is similar to the patient privacy provisions for other drugs in § 314.80(i), though FDA proposes to expand these requirements to nonapplicants.

5. Animal Designated Medical Gas Adverse Event Reporting Requirements

Proposed § 230.230 would contain requirements for submission of adverse event reports related to the use of a designated medical gas in animals. Proposed § 230.230(a) would govern the types of reports that would be required to be submitted to FDA.

Under proposed § 230.230(a)(1), applicants and nonapplicants must submit adverse event reports to FDA as soon as possible but no later than within 15 calendar days of first receiving the information. Reports are required for serious adverse events the applicant or nonapplicant receives from others as well as reports from published literature, regardless of whether the applicant or nonapplicant believes the event is related to the designated medical gas. FDA proposes an exception to the reporting requirements for the death of an animal that was

administered oxygen, unless the applicant or nonapplicant becomes aware of evidence to suggest that the administration of oxygen caused the death. As is the case with human use of oxygen, FDA expects that oxygen will be administered to animals that are in critical condition. For such animals, death is expected to be a common outcome, so unless evidence suggests a causal relationship between oxygen and the death, FDA does not believe that adverse event reporting in that instance will shed new light on the safety of oxygen.

Proposed § 230.230(a)(2) would require that applicants and nonapplicants report adverse events that do not qualify for serious adverse event reporting under paragraph (a)(1) if notified by FDA to do so. This proposed requirement would allow FDA to obtain information regarding other safety signals if the Agency determines additional information is necessary to help protect animal or public health.

As is the case for designated medical gases for human use, FDA would like to clarify that the proposed rule would not require submission of reports for fires associated with oxygen use if the animal patient did not experience an adverse event. Fires associated with oxygen use would be required to be reported if the animal patient experiences an adverse event. Because it is known that oxygen accelerates combustion and that smoking or open flames near an oxygen source can cause a fire, FDA believes it is not necessary to receive reports in which the animal patient did not experience a serious adverse event.

Proposed § 230.230(a)(3) would state that applicants and nonapplicants should not resubmit any adverse event reports obtained from FDA's adverse event reporting database or that FDA forwards to the applicant or nonapplicant, in order to minimize duplication.

The format of adverse event reporting for animal use is addressed in proposed § 230.230(b). FDA proposes to require submission in an electronic format, and that data in electronic submissions conform to the data elements in Form FDA 1932 and the Agency's technical documents on how to provide electronic submissions (e.g., method of transmission and processing, media, file formats, preparation and organization of files). The proposed rule would

allow FDA to issue updated technical documents, as necessary. The most current information on submitting postmarketing safety reports to the Center for Veterinary Medicine (CVM) in electronic format can be found on CVM's webpage at <https://www.fda.gov/IndustryReportAnimalAE> (see, e.g., "Instructions for Electronic Submission of Mandatory Adverse Event Reports to FDA CVM") (Ref. 17). As in the corresponding provision for designated medical gases for human use, under proposed 230.230(b)(2), applicants and nonapplicants would be able to request in writing a temporary waiver of the electronic reporting requirements.

Proposed paragraph (c) contains recordkeeping requirements. Applicants and nonapplicants must maintain records of information related to adverse event reports for up to 5 years from the initial receipt of information. These records must be maintained regardless of whether the information was submitted to FDA. The records must also include raw data, correspondence, and any other information relating to the evaluation and reporting of such information that is received or otherwise obtained by the applicant or nonapplicant. These proposed requirements are generally consistent with the requirements in proposed 230.220(e), though FDA proposes a retention period of 5 years, consistent with other animal safety reporting requirements. FDA also proposes to require that, upon written notice, the applicant or nonapplicant must submit these records to FDA within 5 calendar days after receipt of the notice. Because applicants and nonapplicants would not be required to submit nonserious adverse event reports, retaining the ability to collect records not submitted to the Agency would help FDA address questions that arise as FDA evaluates safety signals. Applicants and nonapplicants must also permit authorized FDA employees to access, copy, and verify these established and maintained records, at reasonable times. These proposed requirements will help facilitate the review of new and emergent safety issues.

6. Part 4 Postmarketing Safety Reporting Requirements

As mentioned above, some medical gases are marketed as part of a combination product. The Agency believes some clarification is needed regarding the applicability of the postmarketing safety reporting requirements in part 4, subpart B to such medical gases.

Because proposed part 230 would only apply to designated medical gases, medical gases under applications submitted under section 505 of the FD&C Act would continue to be subject to the postmarketing safety reporting requirements in part 314. Additionally, if the medical gas is part of a combination product that received marketing authorization (e.g., under an application submitted under section 505 of the FD&C Act), the requirements in part 4, subpart B currently apply. FDA proposes no changes for such products with regard to safety reporting requirements.

As proposed in this section, new part 230 would apply to applicants and nonapplicants of designated medical gases subject to the certification requirements in section 576 of the FD&C Act. As explained in 21 CFR 4.100, part 4, subpart B does not apply to combination products that have not received marketing authorization. Therefore, part 4, subpart B would not apply to designated medical gases that are part of a combination product that did not receive marketing authorization. However, other reporting requirements may apply, e.g., the medical device reporting requirements in 21 CFR part 803 if such combination product includes a device constituent part. Further, if proposed part 230 is finalized, the safety reporting requirements therein would apply to such combination product that includes a designated medical gas.

VI. Proposed Effective Date

FDA proposes that any final rule based on this proposal become effective 18 months after publication in the *Federal Register*. The Agency anticipates that some proposed requirements will result in changes to cylinders as they are returned from service, and that it may take some time for firms to make required changes to all cylinders. We believe that 18 months is an appropriate amount of time to enable firms to make such changes. FDA solicits comment on this proposed compliance date.

VII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would more specifically tailor the current good manufacturing practice requirements for medical gases, add new oxygen labeling requirements, clarify the medical gas certification process, and clarify adverse event reporting requirements, this rule would create small net cost savings for small entities, and we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

This proposed rule, if finalized, would establish, within part 213, CGMP regulations specific to medical gases. These proposed regulations include many of the same categories of requirements as the general drug CGMP regulations but are tailored to reflect differences in how

medical gases are manufactured, packaged, labeled, stored, and distributed. This proposed rule, if finalized, would make limited changes to the labeling requirements of part 201 including requiring that a “no smoking” statement, a “no vaping” statement, and graphic warning symbol be added to oxygen designated medical gas containers to reduce the risk of fire. This proposed rule, if finalized, would codify and clarify the process for obtaining a certification to market designated medical gases. Recommendations for how to request a certification for designated medical gases are currently included in a draft guidance. This proposed rule, if finalized, would establish new postmarketing safety reporting regulations for designated medical gases that would address human and animal use and more specifically reflect the development, manufacturing, and distribution of designated medical gases.

The costs of this proposed rule, if finalized, would be primarily driven by new labeling requirements, regulatory clarification leading to firms becoming compliant with existing requirements, and added CGMP requirements including a requirement for portable cryogenic containers to have a working gauge.

The cost savings of this proposed rule, if finalized, would be primarily driven by removing CGMP requirements that would not apply to medical gases, such as removing certain building and facility requirements, or modifying CGMP requirements so that they would be more well-tailored to medical gases, which may streamline inspections.

Table 1 summarizes the estimated benefits and costs of the proposed rule, if finalized. The annualized benefits would range from \$0.00 million to \$6.48 million with a primary estimate of \$3.24 million over a 10-year span at a 7 percent discount rate. Annualized at a 3 percent discount rate these benefits would range from \$0.00 million to \$6.86 million with a primary estimate of \$3.43 million. The annualized costs would range from \$1.38 million to \$4.95 million with a primary estimate of \$3.03 million at a 7 percent discount rate. Annualized at a 3 percent discount rate these costs would range from \$1.23 million to \$4.77 million with a primary estimate of \$2.88 million.

The present value of the estimated benefits would range from \$0.00 million to \$51.98 million with a primary estimate of \$26.02 million at a 7 percent discount rate and from \$0.00 million to \$65.37 million with a primary estimate of \$32.73 million at a 3 percent discount rate. The present value of the estimated costs would range from \$11.06 million to \$39.71 million with a primary estimate of \$24.33 million at a 7 percent discount rate and from \$11.74 million to \$45.49 million with a primary estimate of \$27.49 million at a 3 percent discount rate.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$millions/year	\$3.24	\$0.00	\$6.43	2020	7%	10	Most benefits are cost savings to industry while the remaining are cost savings for FDA due to a more streamlined inspection process.
		\$3.43	\$0.00	\$6.86	2020	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized \$millions/year	\$3.03	\$1.38	\$4.95	2020	7%	10	
		\$2.88	\$1.23	\$4.77	2020	3%	10	
	Annualized Quantified					7%		
						3%		
Qualitative								
Transfers	Federal Annualized Monetized \$millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized \$millions/year					7%		
						3%		
From/To	From:			To:				
Effects	State, Local or Tribal Government: None Small Business: Not significant Wages: None Growth: None							

FDA conducted a regulatory flexibility analysis of the impact of the proposed rule on small entities. Approximately 41 percent of domestic entities that would be affected by the proposed rule are small according to Small Business Administration (SBA) size standards. We

estimate that the highest single year cost for a firm could be as high as 0.788 percent while the average costs to receipts ratio is 0.007 percent. Therefore, our analysis of the impact of the proposed rule on small entities suggests that small firms will not be significantly affected by the proposed regulation, if finalized.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 18) and at <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h), (j), and (k) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). A description of these provisions is given in the *Description* section of this document with an estimate of the annual reporting, recordkeeping, and third-party disclosure burden. Included in the burden estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including

through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases

Description: This rulemaking is amending existing regulations and establishing new regulatory requirements pertaining to medical gases.

Description of Respondents: Respondents to this information collection are entities who manufacture, process, pack, label, or distribute certain medical gases.

1. Product Jurisdiction and Combination Products; OMB Control No. 0910-0523--Revision.

FDA recognizes that some medical gases are marketed as part of a combination product. For example, a medical gas may be marketed with a device constituent part (for example, a portable liquid oxygen unit or a pressure regulator). Combination products are subject to information collection provisions found in 21 CFR parts 3 and 4, which prescribe content and format requirements associated with marketing applications, together with applicable recordkeeping and reporting requirements.

FDA proposes to revise provisions in part 4 to account for combination products that contain a medical gas, as FDA proposes medical gases to be subject to proposed part 213, and to clarify (where appropriate) applicable medical gases requirements throughout part 4. We believe that the revisions impose no new burden associated with information collection currently approved under OMB control number 0910-0523 and invite comment on our assumptions.

2. Labeling Requirements for Prescription Drugs; OMB Control No. 0910-0572--Revision.

We estimate the burden of the information collection as follows:

Table 2.--Estimated Annual Third-Party Disclosure Burden¹

Activity; Proposed CFR Section	No. of Respondents	No. of Disclosures per Respondent ²	Total Annual Disclosures ²	Average Burden per Disclosure	Total Hours
Labeling of bulk or transport containers used to hold designated medical gases; § 201.161(b)	1,696	2.36	4,000	0.1 (6 minutes)	400

On the container label, identify the owner of a designated medical gas container or a container of a medically appropriate combination of designated medical gases. If the container owner is not the manufacturer, packer, or distributor of the gas, identify that information on the label; § 201.328(d)	1,696	2.36	4,000	0.1 (6 minutes)	400
Total			8,000		800

¹ There are no capital costs or operating and maintenance costs associated with the information collection.

² Totals have been rounded to the nearest whole number.

Regulations in part 201 govern the statement of ingredients and declaration of net quantity of contents with regard to prescription drug product labeling.

The proposed revisions to the regulations would require that firms identify bulk or transport containers with the name of the product contained therein and that containers be accompanied by documentation that identifies the product as meeting applicable compendial standards. Bulk or transport containers are excluded from the proposed definition of final use containers. Because these large containers are removed from the point of care and we do not expect that patients and healthcare practitioners will use them directly to administer designated medical gas, FDA does not believe that firms' bulk or transport containers need to bear the information that we would require under proposed § 201.161(a). However, to prevent mix-ups, it is essential that the identity of the gas inside such containers is evident to individuals who handle and transport the containers. FDA expects that these proposed requirements will help prevent mix-ups and ensure that recipients of medical gases in bulk or transport containers are provided information indicating that such gases meet applicable compendial standards.

Based on our experience with similar information collection, we estimate that 1,696 firms will label 4,000 containers and assume firms will expend 6 minutes (0.1 hours) to identify the containers with the name of the product and place documentation that identifies the product as meeting applicable compendial standards, totaling 400 hours annually.

Proposed § 201.328(d) would provide that the owner of a designated medical gas container or a container of a medically appropriate combination of designated medical gases may be identified on the container. This statement may appear on a separate sticker or decal on the container (that is, it need not be contiguous with other labeling on the container), but if the container owner is not the manufacturer, packer, or distributor of the gas, that information shall be clearly stated. FDA recognizes the complex distribution system for designated medical gases and medically appropriate combinations of designated medical gases and the importance of each entity in the distribution chain being clearly identified so that patients and healthcare professionals can contact the appropriate entity if necessary. We intend for this provision to help ensure that appropriate entities can be contacted about quality issues or adverse events. In addition, the proposed labeling requirement would facilitate the return of cylinders to owners who may not also be medical gas manufacturers. FDA proposes that including the container owner's information will not cause the container owner to be a "relabeler" for purposes of FDA's registration and listing requirements.

Based on our experience with similar information collection, we estimate that 1,696 firms will identify on a designated medical gas container or a container of a medically appropriate combination of designated medical gases the name of the container owner who may not also be the manufacturer, packer, or distributor of the gas. We assume firms would include this label on 4,000 containers and will expend 6 minutes (0.1 hours) to perform this activity, totaling 400 hours annually.

3. Current Good Manufacturing Practice for Medical Gases; OMB Control No. 0910--NEW.

We estimate the burden of the information collection as follows:

Table 3.--Estimated Annual Recordkeeping Burden¹

Activity; Proposed CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper ²	Total Annual Records ²	Average. Burden per Recordkeeping	Total Hours
New Start Up SOP; § 213.42	1,696	1	1,696	13	22,048
SOP Maintenance; § 213.42	1,696	1	1,696	0.65 (39 minutes)	1,102
New Start Up SOP; § 213.208	1,696	1	1,696	13	22,048

SOP Maintenance § 213.208	1,696	1	1,696	0.65 (39 minutes)	1,102
Documentation of completion of training; § 213.25(a)	1,696	10	16,960	0.083 (5 minutes)	1,408
Consultants' records of sufficient education, training, and experience, or any combination thereof; § 213.34	1,696	0.336	571	0.5 (30 minutes)	286
Firms' records of equipment maintenance and cleaning; § 213.67(c)	1,696	43.7676	74,230	0.25 (15 minutes)	18,557
Maintain records for modifications to automatic, mechanical, and electronic equipment; § 213.68(d)	1,696	6.734	11,420	0.25 (15 minutes)	2,855
Receipt and storage of incoming designated medical gases; § 213.82(a)	1,380	417	575,460	0.25 (15 minutes)	143,865
Records of rejected components; § 213.89	1,380	24.2	33,400	0.083 (5 minutes)	2,772
Maintain records for each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected; § 213.122(c)	1,696	43.7676	74,230	0.25 (15 minutes)	18,558
Document results of inspections in the batch production records; § 213.130(e)	1,696	67.334	114,200	0.25 (15 minutes)	28,550
Maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures; § 213.180(d)	1,696	0.27	457	0.25 (15 minutes)	114
Maintain record of equipment cleaning and use log maintenance; § 213.182	1,696	1.76	2,969	0.16 (10 minutes)	475
Maintain records for components, medical gas containers and closures, and labeling; § 213.184	1,696	2.626	4,454	0.33 (19.8 minutes)	1,470
Maintain master production and control records; § 213.186	1,696	13.467	22,840	2	45,680
Maintain batch production and control records; § 213.189	1,696	21.883	37,115	1.3 (78 minutes)	48,250
Maintain record of the investigation; § 213.192(a)	1,696	2.69	4,568	1	4,568
Maintain laboratory records; § 213.194(b) through (e))	1,696	33.667	57,100	0.5 (30 minutes)	28,550
Maintain distribution records; § 213.196	1,696	33.667	57,100	0.25 (15 minutes)	14,275
Maintain written records of each complaint; § 213.198(b)	1,696	6.733	11,420	1	11,420
Total			1,105,278		417,953

¹ There are no capital costs or operating and maintenance costs associated with the information collection.

² Totals have been rounded to the nearest whole number.

FDA proposes to establish part 213 setting forth CGMP requirements applicable to medical gases. If finalized, part 213 would apply to firms that manufacture a medical gas and would also establish requirements applicable to firms that subsequently combine, commingle, refill, or distribute medical gases.

The proposed regulations include recordkeeping requirements pertaining to personnel qualifications and responsibilities of persons who are engaged in the manufacturing, processing, packing, or holding of a medical gas.

Provisions under proposed § 213.42(c) include recordkeeping to document the development and implementation of written procedures to ensure that firms maintain a clean condition for any building used to manufacture, process, pack, or hold a medical gas so as to ensure the safety, identity, strength, quality, and purity of the gas. Firms would need to develop written procedures that apply to maintaining and cleaning buildings. Based on available data, we estimate 1,696 firms will each develop and implement written procedures to maintain and clean buildings. We assume it will take 13 hours to perform this activity, totaling 22,048 hours annually. Firms would also maintain these procedures. Based on available data, we estimate 1,696 firms would each maintain written procedures to maintain and clean buildings. We assume it will take 39 minutes (0.65 hours) to perform this activity, totaling 1,102 hours annually.

Similarly, under proposed § 213.208, firms would be required to develop and implement written procedures for the holding, testing, and use of salvaged medical gases. Based on available data, we estimate 1,696 firms will develop and implement written procedures for the holding, testing, and use of salvaged medical gases. We assume it will take 13 hours for firms to perform this activity, totaling 22,048 hours annually. Based on available data, 1,696 firms will prepare written procedures (1 procedure each) for the holding, testing, and use of salvaged

medical gases. We assume it takes 0.65 hours to perform this activity, totaling 1,102 hours annually.

The proposed regulations would provide that employee training be included in the firm operations. Recordkeeping would be established to demonstrate that qualified individuals conduct training on a continuing basis and with sufficient frequency to allow employees to remain familiar with applicable requirements. Based on available data, we estimate that 1,696 firms will prepare written documentation pertaining to employee training. We assume 10 employees per firm will create 16,960 records (10 records per firm) and that it will take 5 minutes (0.083 hours) to prepare the records, for a total of 1,408 hours annually.

Under proposed § 213.34, records demonstrating that consultants have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained will be required. Based on available data, we estimate that 1,696 firms will maintain 571 records of consultants' education, training, and experience, or any combination thereof and assume it will take 30 minutes (0.5 hours) to perform this activity, totaling 286 hours annually.

Based on available data, we estimate that 1,696 firms will maintain 74,230 records of equipment maintenance and cleaning and assume it will take 15 minutes (0.25 hours) to perform this activity, totaling 18,557 hours annually.

Based on available data, we estimate 1,696 firms will develop and implement 11,420 written procedures for automatic, mechanical, and electronic equipment and assume firms will expend 15 minutes (0.25 hours) to perform this activity, totaling 2,855 hours annually.

As provided for in the proposed regulations, if an incoming designated medical gas is obtained from a supplier other than the original manufacturer, the shipment would also need to include specific information. To ensure the reliability of appropriate assessment and testing, firms will be required to establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures. Based on

assumptions found in our Preliminary Regulatory Impact Analysis (PRIA), we estimate that 1,380 firms would verify and document records upon receipt of a designated medical gas. We assume firms will maintain 575,460 records (417 records each (1 delivery per week of oxygen for 1 year (52 deliveries) plus 1 delivery per night of nitrogen for 1 year (365 deliveries))). We further assume firms will expend 15 minutes (0.25 hours) each (104 hours in total for each firm) to perform this activity, totaling approximately 143,865 hours annually.

Proposed § 213.89 would require that firms identify and control rejected components, containers, and closures under a quarantine system designed to prevent their use in operations for which they are unsuitable. Proposed § 213.89 also applies to incoming designated medical gases. Quarantine systems would not need to include physical quarantining because other methods can adequately ensure that unsuitable products are not used. Based on assumptions found in section II.F.4.b of the PRIA, we estimate that 1,380 downstream firms would need to assess and document 33.4 million medical gas components, containers, and closures annually. We assume that firms would reject 0 to 0.1 percent of all containers. These firms will maintain a total of 33,400 records of rejected components and we assume will expend 5 minutes (0.083 hours) to perform this activity, totaling 2,772 hours annually.

Under proposed § 213.122(c), firms would need to maintain records for each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected. Based on available data, we estimate 1,696 firms will prepare 74,230 records to document each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected. We assume it will take 15 minutes (0.25 hours) to perform this activity, totaling 18,558 hours annually.

Under proposed 213.130(e), firms would need to document results of inspections concerning packaging and labeling in the batch production records. Based on available data, we estimate 1,696 firms will document results of inspections in the batch production records in

approximately 114,200 records. We assume it will take 15 minutes (0.25 hours) per record to perform this activity, totaling 28,550 hours annually.

As described in section V.B.11 of this document and proposed § 213.180(d), firms would need to maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures. Based on available data, we estimate 1,696 firms will prepare 457 records. We assume it will take 15 minutes (0.25 hours) to perform this activity, totaling 114 hours annually.

Under proposed § 213.182 and as described in section V.B.11 of this document, firms would need to maintain a written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use. Based on available data, we estimate 1,696 firms will prepare 2,969 records documenting major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use. We assume it will take 10 minutes (0.16 hours) to perform this activity, totaling 475 hours annually.

As described in section V.B.11 of this document and under proposed § 213.184, firms would need to maintain certain records concerning components, medical gas containers and closures, and labeling. Based on assumptions found in our PRIA, we estimate 1,696 firms will prepare 4,454 records for components, medical gas containers and closures, and labeling. We assume firms will expend 19.8 minutes (0.33 hours) to perform this activity, totaling 1,470 hours annually.

As discussed in section V.B.11 of this document and estimates for the number of firms calculated throughout the PRIA, under proposed § 213.186, to ensure uniformity from batch to batch, firms would need to prepare, date, and sign master production and control records for each medical gas. Based on data from existing information collection requests and estimates for the number of firms calculated throughout the PRIA, we estimate 1,696 firms will prepare and

maintain approximately 22,840 master production and control records and assume it will require 2 hours for firms to perform this activity, totaling 45,680 hours annually.

Under proposed § 213.189 and as described in section V.B.11 of this document, firms would need to maintain batch production and control records. These records would need to include documentation that the firm has accomplished each significant step in the manufacturing, processing, packing, or holding of the medical gas produced. Based on data from existing information collection requests and estimates for the number of firms calculated throughout the PRIA, we estimate 1,696 firms will prepare and maintain 37,115 batch production and control records. We assume it will require 78 minutes (1.3 hours) for firms to perform this activity, totaling 48,250 hours annually.

Section V.B.11 of this document and proposed § 213.192(a) describe production record review. Per paragraph (a), firms would need to maintain a written record of the investigation and include the conclusions and followup. Based on data from existing information collection requests and estimates for the number of firms calculated throughout the PRIA, we estimate 1,696 firms will prepare and maintain 4,568 laboratory records and that it will require 1 hour for firms to perform this activity, totaling 4,568 hours annually.

Under proposed § 213.194(b) through (e) and as described in section V.B.11 of this document, firms would need to maintain certain laboratory records. Based on available data, we estimate 1,696 firms will prepare and maintain 57,100 laboratory records and assume it will require 30 minutes (0.5 hours) for firms to perform this activity, totaling 28,550 hours annually.

As described in section V.B.11 of this document, proposed § 213.196 describes certain proposed requirements for distribution records. Based on available data, we estimate 1,696 firms will prepare and maintain 57,100 distribution records and assume it will require 15 minutes (0.25 hours) for firms to perform this activity, totaling 14,275 hours annually.

As discussed under proposed § 213.198(b), firms would be required to maintain written records of each complaint regarding medical gases. Our full discussion is shown in section

V.B.11 of this document. Based on assumptions found in our PRIA, we estimate 1,696 firms will maintain 11,420 records of complaints. We assume it will require approximately 1 hour for firms to perform this activity, totaling 11,420 hours annually.

4. Certification Process and Postmarketing Quality and Safety Reporting; OMB Control No.

0910-NEW.

Table 4.--Estimated Annual Reporting Burden¹

Activity; Proposed CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Submission of certification requests and certification form that includes any resubmissions and amendments to pending requests; § 230.50	5	1	5	3	15
Submission of supplements to certification requests and other changes; § 230.70	4	1	4	3	12
Submission of requests to transfer ownership of certification, including new address and the owner's submission of any change in the conditions in the granted certification; § 230.72	2	2	4	2	8
Annual reports; § 230.80	50	2.16	108	2	216
Field alert reports; § 230.205	1,380	0.002	3	8	24
CDER: Submission of ICSRs (§ 230.220(a) through (d))	1,430	0.12	172	6	1,032
CDER's maintenance of records for human designated medical gas ICSR requirements (§ 230.220(e))	1,430	0.48	686	16	10,976
CVM's recordkeeping requirements related to adverse event reports (§ 230.230(c))	1,696	0.0044	7.5	5	37.5
CVM: Submission of adverse event reports; § 230.230	1,696	0.0044	7.5	5	37.5
CVM: Waiver request from electronic submission requirement; § 230.230	1,696	0.0044	7.5	5	37.5
Total			1,004.5		12,395.5

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

² Totals have been rounded to the nearest whole number.

Proposed § 230.50 (see section V.C.2 of this document) would establish the general requirements for requesting a designated medical gas certification for all submission types and would outline the information that must be included in certification request submissions.

The proposed regulations would require applicants to include facility information in certification requests. Such information would include, among others, name and address of the original manufacturing facility or facilities where the gas is or will be manufactured.

Proposed section 230.50 would also provide for the submission of additional information if FDA deems it appropriate to determine whether a medical gas meets the definition of a designated medical gas. This information would generally be in the form of a written request by FDA for the additional information.

Based on assumptions found in our PRIA, we estimate that five respondents will submit a total of five certification requests annually, including certification forms for original and resubmissions. We assume each certification request will require 3 hours to prepare and submit, totaling 15 hours annually.

Under proposed § 230.65, applicants would be allowed to withdraw a certification request that has not been deemed granted. An applicant could notify FDA that it withdraws its certification request at any time before the certification is deemed granted. Upon an applicant's withdrawal of a certification request, FDA would retain the certification request, and if the applicant requests a copy via FOIA request, FDA would provide it pursuant to the fee schedule in FDA's public information regulations. Since the passage of FDASIA, FDA has received several certification requests but has not received any withdrawal requests. FDA has no other data on which to provide a burden estimate. Therefore, the Agency does not expect to receive withdrawal requests except in exceedingly rare situations.

Proposed § 230.70, as discussed in section V.C.3 of the proposed rule would require applicants to submit a supplement if any information in the granted certification has changed. The proposed regulation would prescribe information to be included in a supplement submission.

Based on our experience with similar information collection, we estimate four applicants will submit supplements and assume, each submission will require 3 hours to prepare, totaling 12 hours annually.

Proposed § 230.72 would govern changes in ownership of a granted certification. An example of when a change in ownership could occur is during a merger or acquisition. Upon a change in ownership, the regulations would require that both the new and previous owner notify FDA.

Based on related submissions received by FDA over the last few years and averaged accordingly, we estimate two respondents will submit four letters or other supporting documents, and assume it will take 2 hours to complete this task, totaling 8 hours annually.

To assist respondents with the proposed submission requirements associated with proposed § 230.80 (annual reports), we are developing an annual report form.

Based on our records and informal requests received upon announcing this rulemaking, we estimate that 50 applicants will submit to FDA 108 annual reports (a total of 108 reports). We assume firms will expend 2 hours to perform this activity, totaling 216 hours annually.

Our estimate associated with proposed requirements in § 230.205 for field alert reporting for designated medical gases is based on our experience with similar reports that FDA received in 2019 and 2020.

We estimate that 1,380 applicants and nonapplicants will submit to FDA three FARs. We assume respondents will expend approximately 8 hours to perform this activity, totaling 24 hours annually.

Proposed § 230.210 would require that applicants and nonapplicants promptly review all safety information that the applicant or nonapplicant receives or otherwise obtains from any source (including both foreign and domestic sources). Applicants and nonapplicants would generate reports from their review and submit them under proposed §§ 230.220 and 230.230.

As described under proposed § 230.220(a) through (d) (see section V.D.4 of this document), firms would be required to submit ICSRs associated with the use of a designated medical gas in humans.

Proposed § 230.220 (see section V.D.4 of this document) would contain requirements for submission of ICSRs associated with the use of a designated medical gas in humans. Under proposed § 230.220(a)(1), applicants and nonapplicants would be required to submit each ICSR as soon as possible, but no later than 15 calendar days from the date the applicant or nonapplicant has met the reporting criteria under proposed § 230.220(b) and acquired a minimum data set for an ICSR for that adverse event.

Under proposed § 230.220(a)(3), applicants and nonapplicants would submit new information they receive or otherwise obtain about a previously submitted ICSR to FDA. The proposed regulation would prescribe reporting schedules to ensure FDA becomes aware of any new information that arises about the adverse event.

Based on assumptions found in our PRIA and a review of safety report data, we estimate that 1,430 applicants and nonapplicants will submit to FDA 172 ICSRs annually. We assume it will take 6 hours for respondents to perform this activity, totaling 1,032 hours annually.

Proposed § 230.220(b) would describe the types of ICSRs that applicants and nonapplicants would need to report for human use. Under proposed § 230.220(b)(1), applicants and nonapplicants would be required to submit ICSRs for serious adverse events. Under proposed § 230.220(b)(2), FDA proposes to require an applicant to report to FDA, in a timeframe established by FDA, ICSRs for any adverse events that would not be required under proposed § 230.220(b)(1) upon notification by FDA.

Proposed § 230.220(e) would prescribe content and format requirements for records pertaining to human designated medical gas adverse events. For a period of 10 years from the initial receipt of information, each applicant or nonapplicant would be required to maintain records of information relating to adverse events, whether or not submitted to FDA. These records would need to include raw data, correspondence, and any other information relating to evaluating and reporting adverse event information that is received or otherwise obtained by the applicant or nonapplicant. Upon written notice by FDA, the applicant or nonapplicant would

need to submit any and all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant would need to permit any authorized FDA employee, at reasonable times, to access, copy, and verify the established and maintained records described in this section.

Based on available data, we estimate that 1,430 manufacturers will create 686 records pertaining to human designated medical gas requirements and that it would take approximately 16 hours to perform this activity, totaling 10,976 hours.

Proposed § 230.220(c) and (d) would include additional requirements for the content and format of ICSRs.

Based on available data, we assume all firms (1,696) will distribute designated medical gases for human and animal use and invite comment on our assumption.

Under proposed § 230.230(a)(1), an applicant or nonapplicant would need to submit serious adverse events related to the use of a designated medical gas in animals to FDA as soon as possible but no later than 15 calendar days from first receiving the information. The applicant or nonapplicant would need to submit the report to FDA in electronic format as described under proposed § 230.230(b)(1) of this section, unless the applicant or nonapplicant obtains a waiver under proposed § 230.230(b)(2) of this section or FDA requests the report in an alternate format.

Under proposed § 230.230(a)(2), upon notification by FDA, applicants and nonapplicants would need to submit reports of adverse events associated with the use of a designated medical gas in animals that do not qualify for reporting under proposed § 230.230(a)(1) of this section. The notice would specify the adverse events to be reported and the reason for requiring the reports.

We estimate approximately 7.5 records will be submitted per year and estimate that it will take approximately 5 hours to perform this activity, totaling 37.5 hours. We also estimate that approximately 7.5 reports will be maintained yearly and estimate it will take 5 hours to perform this activity, totaling 37.5 hours.

Under proposed § 230.230(b)(2), an applicant or nonapplicant could request, in writing, a temporary waiver of the electronic submission requirements under proposed § 230.230(b)(1). An applicant or nonapplicant would need to provide the initial request by telephone or email to CVM's Division of Veterinary Product Safety, with prompt written followup submitted as a letter to the granted certification or certifications. FDA would grant waivers on a limited basis for good cause shown. If FDA grants a waiver, the applicant or nonapplicant would need to comply with the conditions for reporting specified by FDA upon granting the waiver.

We estimate approximately 7.5 waiver requests will be submitted annually and estimate it will take 5 hours to perform this activity, totaling 37.5 hours annually.

To ensure that comments on information collection are received, OMB recommends that written comments be through reginfo.gov (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the PRA (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the *Federal Register*.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the proposed rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

*1. Food and Drug Administration (FDA) draft guidance for industry “Certification Process for Designated Medical Gases,” November 2015, available at <https://www.fda.gov/media/85013/download>.

*2. FDA, Medical Gas Regulation Public Workshops, available at <https://www.fda.gov/drugs/news-events-human-drugs/medical-gas-regulation-public-workshops>.

3. Lacasse, Y., M. Légaré, and F. Maltais, “E-cigarette Use in Patients Receiving Home Oxygen Therapy,” *Canadian Respiratory Journal*, vol. 22, no. 2, 83-85, March/April 2015. <https://downloads.hindawi.com/journals/crj/2015/215932.pdf>.

*4. Benowitz, N.M., “E-cigarette Explosion in a Patient Room,” *PSNet*, April 2019. <https://psnet.ahrq.gov/web-mm/e-cigarette-explosion-patient-room>.

5. Fire & Rescue NSW, “Fire Research Report--E-Cigarette Fire Risks and Reported Incidents,” January 30, 2015.

<https://www.icao.int/safety/dangerousgoods/dgpwg15/dgpwg.15.ip.004.2.en.app.pdf>.

6. Rudy, S.F. and E.L. Durmowicz, “Electronic Nicotine Delivery Systems: Overheating, Fires and Explosions,” *Tobacco Control*, 26:10-18, 2017.

<https://tobaccocontrol.bmj.com/content/tobaccocontrol/26/1/10.full.pdf>.

*7. FDA, Response to petition submitted by Compressed Gas Association, Docket No. 87P-0167/CP1, September 19, 1996.

*8. FDA, Public Health Advisory, “Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities,” March 2001, available at <https://www.fda.gov/media/70999/download>.

*9. Kreiter, P., T.G. Bizjak, and R.L. Friedman, “Preventing Patients From Receiving Leaking or Empty Containers of Medical Gas: A Review of Inspectional Findings From 2003 to 2021,” CDER Office of Manufacturing Quality, December 2021, U.S. Food and Drug Administration.

*10. CDER, Manual of Policies and Procedures 5310.7 Rev. 1, “Acceptability of Standards from Alternative Compendia (BP/EP/JP),” available at <https://www.fda.gov/media/72412/download>.

*11. FDA guidance for industry “Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration,” November 2014, available at <https://www.fda.gov/media/89926/download>.

*12. FDA draft guidance for industry “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines,” March 2001, available at <https://www.fda.gov/media/73593/download>.

*13. FDA guidance for industry “Field Alert Report Submission--Questions and Answers,” July 2021, available at <https://www.fda.gov/media/114549/download>.

*14. FDA, Compliance Program Guidance Manual 7356.002E, “Compressed Medical Gases,” March 15, 2015, available at <https://www.fda.gov/media/75194/download>.

*15. FDA draft guidance for industry “Providing Submissions in Electronic Format-- Postmarketing Safety Reports,” June 2014, available at <https://www.fda.gov/media/71176/download>.

16. International Council on Harmonization, MedDRA, available at <https://www.ich.org/page/meddra>.

*17. FDA, Veterinary Adverse Event Reporting for Manufacturers, available at <https://www.fda.gov/IndustryReportAnimalAE>.

*18. FDA, Preliminary Regulatory Impact Analysis: Current Good Manufacturing Practice, Certification, Postmarketing Safety Reporting, and Labeling Requirements for Certain Medical Gases, available at <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.

List of Subjects

21 CFR Part 4

Biologics, Drugs, Human cells and tissue-based products, Medical devices.

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 213

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 230

Administrative practice and procedure, Animal drugs, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, the Food and Drug Administration proposes to amend chapter I of title 21 of the Code of Federal Regulations as follows:

PART 4--REGULATION OF COMBINATION PRODUCTS

1. The authority citation for part 4 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360l, 360hh-360ss, 360aaa-360bbb, 360ddd, 360ddd-1, 371(a), 372-374, 379e, 381, 383, 394; 42 U.S.C. 216, 262, 263a, 264, 271.

2. Revise § 4.2 to read as follows:

§ 4.2 How does FDA define key terms and phrases in this subpart?

The terms listed in this section have the following meanings for purposes of this subpart:

Biological product has the meaning set forth in § 3.2(d) of this chapter. A biological product also meets the definitions of either a drug or device as these terms are defined under this section.

Combination product has the meaning set forth in § 3.2(e) of this chapter.

Constituent part is a drug, device, or biological product that is part of a combination product.

Co-packaged combination product has the meaning set forth in § 3.2(e)(2) of this chapter.

Current good manufacturing practice operating system means the operating system within an establishment that is designed and implemented to address and meet the current good manufacturing practice requirements for a combination product.

Current good manufacturing practice requirements means the requirements set forth under § 4.3(a) through (e).

Device has the meaning set forth in § 3.2(f) of this chapter. A device that is a constituent part of a combination product is considered a finished device within the meaning of the QS regulation.

Drug has the meaning set forth in § 3.2(g) of this chapter and includes medical gas as defined in section 575(2) of the Federal Food, Drug, and Cosmetic Act. Medical gas includes designated medical gases as defined in section 575(1) of the Federal Food, Drug, and Cosmetic Act and medical gases approved under section 505 of the Federal Food, Drug, and Cosmetic Act. A drug other than a medical gas that is a constituent part of a combination product is considered a drug product within the meaning of the drug current good manufacturing practice regulations (CGMPs). A drug that is a medical gas that is a constituent part of a combination product is considered a medical gas within the meaning of the medical gas CGMPs.

Drug CGMPs refers to the current good manufacturing practice regulations set forth in parts 210 and 211 of this chapter.

HCT/Ps refers to human cell, tissue, and cellular and tissue-based products, as defined in § 1271.3(d) of this chapter. An HCT/P that is not solely regulated under section 361 of the Public Health Service Act may be a constituent part of a combination product. Such an HCT/P is

subject to part 1271 of this chapter and is also regulated as a drug, device, and/or biological product.

Manufacture includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage.

Medical gas CGMPs refers to the current good manufacturing practice regulations set forth in part 213 of this chapter.

QS regulation refers to the quality system regulation in part 820 of this chapter.

Single-entity combination product has the meaning set forth in § 3.2(e)(1) of this chapter.

Type of constituent part refers to the category of the constituent part, which can be either a biological product, a device, or a drug, as these terms are defined under this section.

3. Amend § 4.3 by revising paragraphs (a), (c), and (d), and adding paragraph (e) as follows:

§ 4.3 What current good manufacturing practice requirements apply to my combination product?

(a) The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part other than a medical gas;

(c) The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to which those requirements would apply if that constituent part were not part of a combination product;

(d) The current good tissue practice requirements including donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P; and

(e) The current good manufacturing practice requirements in part 213 of this chapter apply to a combination product that includes a drug that is a medical gas.

4. Amend § 4.4 by:

- a. Revising paragraphs (b)(1) introductory text, (b)(2) introductory text, and (e);
- b. Redesignating paragraphs (b)(3) and (b)(4) as (b)(4) and (b)(5), respectively; and
- c. Adding new paragraph (b)(3).

The revisions and addition read as follows:

§ 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

(b) ***

(1) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs or the medical gas CGMPs, as applicable, the following provisions of the QS regulation must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QS regulation need be made:

(2) If the combination product includes a device constituent part and a drug constituent part other than a medical gas, and the current good manufacturing practice operating system has been shown to comply with the QS regulation, the following provisions of the drug CGMPs must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the drug CGMPs need be made:

(3) If the combination product includes a device constituent part and a drug constituent part that is a medical gas, and the current good manufacturing practice operating system has been

shown to comply with the QS regulation, the following provisions of the medical gas CGMPs must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the medical gas CGMPs need be made:

- (i) Section 213.84 of this chapter. Testing and approval or rejection of components, containers, and closures.
- (ii) Section 213.94 of this chapter. Medical gas containers and closures.
- (iii) Section 213.122 of this chapter. Materials examination and usage criteria.
- (iv) Section 213.165 of this chapter. Testing and release for distribution.
- (v) Section 213.166 of this chapter. Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act.
- (vi) Section 213.204 of this chapter. Returned medical gases.
- (vii) Section 213.208 of this chapter. Salvaging of medical gases.

(e) The requirements set forth in this subpart and in parts 210, 211, 213, 820, 600 through 680, and 1271 of this chapter listed in § 4.3, supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event of a conflict between regulations applicable under this subpart to combination products, including their constituent parts, the regulations most specifically applicable to the constituent part in question shall supersede the more general.

PART 16--REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

5. The authority citation for part 16 continues to read as follows:

Authority: 15 U.S.C. 1451-1461; 21 U.S.C. 141-149, 321-394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201-262, 263b, 364.

6. In § 16.1, revise paragraph (b)(2) by numerically adding an entry for “§ 230.150(b)” to read as follows:

§ 16.1 Scope.

(b) ***

(2) ***

§ 230.150(b), relating to revocation of the grant of a certification for a designated medical gas.

PART 201--LABELING

7. The authority citation for part 201 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc-1, 360ddd, 360ddd-1, 360ee, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

8. In § 201.1, revise paragraph (b) to read as follows:

§ 201.1 Drugs; name and place of business of manufacturer, packer, or distributor.

(b) As used in this section, and for purposes of section 502(a) and (b)(1) of the Federal Food, Drug, and Cosmetic Act, the manufacturer of a drug product is the person who performs all of the following operations that are required to produce the product:

(1) Mixing,

(2) Granulating,

(3) Milling,

(4) Molding,

(5) Lyophilizing,

(6) Tableting,

(7) Encapsulating,

(8) Coating,

(9) Sterilizing,

(10) Filling sterile or aerosol drugs into dispensing containers, and

(11) With respect to a medical gas, fabricating the gas by chemical reaction, physical separation, compression of atmospheric air, purification (e.g., re-processing an industrial gas into a medical gas), by combining two or more distinct medical gases, or by other process.

9. In § 201.10, revise paragraph (d)(2) to read as follows:

§ 201.10 Drugs; statement of ingredients.

(d)***

(2) A statement of the percentage of an ingredient in a drug shall, if the term *percent* is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in volume at 68 °F. (20 °C.), if the ingredient is a solid and the drug is a liquid; percent volume in volume at 68 °F. (20 °C.), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C.); and percent volume in volume if the ingredient is a designated medical gas (as defined in § 201.161(c)(1)).

10. In § 201.51, revise paragraphs (a) and (b) to read as follows:

§ 201.51 Declaration of net quantity of contents.

(a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be

expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, in terms of fluid measure if the drug is liquid, or in terms of volume measure if the drug is a designated medical gas (as defined in § 201.161(c)(1)) or a medically appropriate combination of designated medical gases in a gaseous state. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.

(b) Statements of weight of the contents shall in the case of prescription drugs be expressed in terms of avoirdupois pound, ounce, and grain or of kilogram, gram, and subdivisions thereof. A statement of liquid measure of the contents shall in the case of prescription drugs other than designated medical gases and medically appropriate combinations thereof be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, fluid-ounce, and fluid-dram subdivisions thereof, or of the liter and milliliter, or cubic centimeter, and shall express the volume at 68° F. (20° C.). A statement of the liquid measure of the contents in the case of insulin-containing drugs shall be expressed in terms of the liter and milliliter, or cubic centimeter, and shall express the volume at 68° F. (20° C.). A statement of the measure of the contents shall in the case of designated medical gases (as defined in § 201.161(c)(1)) and medically appropriate combinations thereof be expressed as follows:

(1) If in a gaseous state in a high pressure container, it shall be expressed in liters or cubic feet based on the filled pressure at 70° F.;

(2) If in a liquefied compressed gas state in a high pressure container, it shall be expressed in gaseous liters or by an appropriate net weight statement;

(3) If in a liquefied state in a portable cryogenic container, it shall be expressed in gaseous liters, liquid liters (if identified as a liquid measure), gallons, or by an appropriate net weight statement at the time of fill;

(4) If in a bulk or transport container (as defined in § 201.161(c)(3)), labeling for net quantity of contents is not required;

11. In § 201.105 revise the introductory text paragraph to read as follows:

§ 201.105 Veterinary drugs.

A drug subject to the requirements of section 503(f)(1) of the act shall be exempt from section 502(f)(1) of the act if it is a designated medical gas (as defined in § 201.161(c)(1)) or a medically appropriate combination of designated medical gases and is in compliance with § 201.161, or if all the following conditions are met:

12. Revise § 201.161 to read as follows:

§ 201.161 Medical gases.

(a) The requirements of sections 503(b)(4) and 502(f) of the Federal Food, Drug, and Cosmetic Act are deemed to have been met for a designated medical gas or a medically appropriate combination of designated medical gases if the labeling on its final use container bears the following:

(1) In the case of oxygen:

(i) A warning statement providing that uninterrupted use of high concentrations of oxygen over a long duration, without monitoring its effect on oxygen content of arterial blood, may be harmful; that oxygen should not be used on patients who have stopped breathing unless used in conjunction with resuscitative equipment; and, in the case of oxygen that may be provided without a prescription for use in the event of depressurization or other environmental oxygen deficiency, or for oxygen deficiency or for use in emergency resuscitation when administered by properly trained personnel, a warning statement providing that oxygen may be used for emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation, and that for all other medical applications a prescription is required.

(ii) A clear and prominent warning containing the statements “No Smoking” and “No Vaping” and a graphic symbol conveying that smoking, vaping, and open flames near oxygen are dangerous.

(2) In the case of a designated medical gas other than oxygen, and in the case of medically appropriate combinations of any designated medical gases:

(i) A warning statement providing that the administration of the gas or gas combination (as applicable) may be hazardous or contraindicated; and that the gas or gas combination (as applicable) should be used only by or under the supervision of a licensed practitioner who is experienced in the use and administration of the gas or gas combination (as applicable) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken.

(ii) The symbol “Rx only.”

(3) Appropriate directions and warnings concerning storage and handling.

(b) A designated medical gas or medically appropriate combination of designated medical gases in a bulk or transport container must be identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards.

(c) For purposes of this section:

(1) A “designated medical gas” means a drug that:

(i) Is manufactured or stored in a liquefied, nonliquefied, or cryogenic state;

(ii) Is administered as a gas; and

(iii) Meets the definition in section 575(1) of the Federal Food, Drug, and Cosmetic Act.

(2) A “final use container” means a container that is for direct use or access by a patient or healthcare provider to administer a designated medical gas or medically appropriate combination of designated medical gases. The term “final use container” does not include bulk

or transport containers and does not include containers that are described in § 868.5655 of this chapter.

(3) A “bulk or transport container” means a container used to transport or store designated medical gases or medically appropriate combinations of designated medical gases and that is not used directly to administer such gases to a patient.

13. In § 201.328, revise paragraph (a)(1) introductory text and add paragraph (d) to read as follows.

§ 201.328 Labeling of medical gas containers.

(a)***

(1) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. Such label must meet the requirements of **§ 213.94(e)(3) of this chapter and the following additional requirements.**

(d) Notwithstanding § 201.1, a container filled with a designated medical gas (as defined in § 201.161(c)(1)) or medically appropriate combination of designated medical gases may bear a statement identifying the name of the owner of the container or the address to which the container should be returned after use. Such statement may appear on a separate sticker or decal. If the owner of the medical gas container is not the manufacturer, packer, or distributor of the designated medical gas or medically appropriate combination of designated medical gases, that shall be clearly stated on the container. The addition of such statement shall not cause the owner of the cylinder to be a “relabeler” for purposes of registration and listing under part 207 of this chapter.

**PART 210--CURRENT GOOD MANUFACTURING PRACTICE IN
MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS;
GENERAL**

14. The authority citation for part 210 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 360ddd, 360ddd-1, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

15. In § 210.1, revise paragraphs (a) and (b) to read as follows:

§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211, 213, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 213, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

16. In § 210.2, revise paragraphs (a) and (b) to read as follows:

§ 210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in parts 211, 213, 225, and 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter,

the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in parts 211, 213, 225, 226, 600 through 680, and 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which the person is engaged.

PART 211--CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

17. The authority citation for part 211 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 360ddd, 360ddd-1, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

18. In § 211.1, revise paragraph (a) to read as follows:

§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs and medical gases as defined in § 213.3(b)(12) of this chapter) for administration to humans or animals.

19. In § 211.94, remove paragraph (e).

20. In § 211.125 revise paragraph (c) to read as follows:

§ 211.125 Labeling issuance.

(c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow

preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 211.122(g)(2).

21. In § 211.132, revise paragraph (c)(1) introductory text to read as follows:

§ 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(c)***

(1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

22. In § 211.170, revise paragraph (b) introductory text to read as follows:

§ 211.170 Reserve samples.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of

reserve sample deterioration shall be investigated in accordance with § 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product.

The retention time is as follows:

23. Revise § 211.196 to read as follows:

§ 211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product.

24. Add part 213 to subchapter C to read as follows:

PART 213--CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICAL GASES

Subpart A--General Provisions

Sec.

213.1 Scope.

213.3 Definitions.

Subpart B--Organization and Personnel

213.22 Responsibilities of quality unit.

213.25 Personnel qualifications and responsibilities.

213.34 Consultants.

Subpart C--Buildings and Facilities

213.42 Design and construction features.

Subpart D--Equipment

213.63 Equipment design, size, and location.

213.65 Equipment construction.

213.67 Equipment maintenance and cleaning.

213.68 Automatic, mechanical, and electronic equipment.

Subpart E--Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures

213.80 General requirements.

213.82 Receipt and storage of incoming designated medical gases.

213.84 Testing and approval or rejection of components, containers, and closures.

213.89 Rejected components, incoming designated medical gases, and medical gas containers and closures.

213.94 Medical gas containers and closures.

Subpart F--Production and Process Controls

213.100 Written procedures; deviations.

213.101 Charge-in of components and incoming designated medical gases.

213.110 Sampling and testing of in-process materials.

Subpart G--Packaging and Labeling Control

213.122 Materials examination and usage criteria.

213.125 Labeling issuance.

213.130 Packaging and labeling operations.

Subpart H--Holding and Distribution

213.150 Warehousing and distribution procedures.

Subpart I--Laboratory Controls

213.160 General requirements.

213.165 Testing and release for distribution.

213.166 Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act.

Subpart J--Records

- 213.180 General requirements.
- 213.182 Equipment cleaning and use log.
- 213.184 Records for components, medical gas containers and closures, and labeling.
- 213.186 Master production and control records.
- 213.189 Batch production and control records.
- 213.192 Production record review.
- 213.194 Laboratory records.
- 213.196 Distribution records.
- 213.198 Complaint files.

Subpart K--Returned and Salvaged Medical Gases

- 213.204 Returned medical gases.
- 213.208 Salvaging of medical gases.

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360b, 360ddd, 360ddd-1, 371, 374.

Subpart A--General Provisions

§ 213.1 Scope.

The regulations in this part contain the minimum current good manufacturing practice for preparation of medical gases for administration to humans or animals.

§ 213.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(2) *Batch* means a specific quantity of a medical gas or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) *Commingling or commingled* refers to the act of combining one lot of designated medical gas or component with another lot or lots of the same designated medical gas or component.

(4) *Component* means any ingredient intended for use in the manufacture of a medical gas, including those that may not appear in such gas. It does not include an incoming designated medical gas.

(5) *Designated medical gas* means a drug that is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; is administered as a gas; and is defined in section 575(1) of the Federal Food, Drug, and Cosmetic Act.

(6) *FDA* means the Food and Drug Administration.

(7) *In-process material* means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the medical gas.

(8) *Incoming designated medical gas* means a designated medical gas received from one source that is commingled with the same gas from another source, used in a medically appropriate combination of designated medical gases or in the production of another medical gas, or further distributed.

(9) *Lot* means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a medical gas produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(10) *Lot number, control number, or batch number* means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the

manufacture, processing, packing, holding, and distribution of a batch or lot of medical gas, or other material can be determined.

(11) *Manufacture, processing, packing, or holding of medical gases* includes packaging and labeling operations, testing, and quality control.

(12) *Medical gas* has the meaning given the term in section 575(2) of the Federal Food, Drug, and Cosmetic Act.

(13) *Original manufacturer* means the person or entity that initially produces a designated medical gas by chemical reaction, physical separation, compression of atmospheric air, purification (e.g., re-processing an industrial gas into a medical gas), or other means.

(14) *Quality unit* means any person or persons designated with the authority and responsibility for overall quality management and other responsibilities as defined in § 213.22.

(15) *Strength* means:

(i) The concentration of the medical gas (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

(ii) The potency, that is, the therapeutic activity of the medical gas as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

Subpart B--Organization and Personnel

§ 213.22 Responsibilities of quality unit.

(a) There shall be a quality unit that shall have the responsibility and authority to approve or reject all components, medical gas containers and closures, in-process materials, packaging material, labeling, and medical gases, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality unit shall be responsible for approving or rejecting medical gases manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, medical gas containers and closures, packaging materials, in-process materials, and medical gases shall be available to the quality unit.

(c) The quality unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the medical gas.

(d) The responsibilities and procedures applicable to the quality unit shall be in writing; such written procedures shall be followed.

(e) Quality unit personnel may perform other functions provided appropriate written controls are in place to ensure any other functions are performed separately from quality unit responsibilities and such other functions do not interfere with the quality unit's responsibilities or subordinate the quality unit's responsibilities to any other unit.

§ 213.25 Personnel qualifications and responsibilities.

(a) Each person engaged in the manufacture, processing, packing, or holding of a medical gas shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with current good manufacturing practice requirements applicable to them. Written documentation shall be maintained demonstrating the completion of employee training, and shall include the date of the training, the type of the training, and the results of any completion criteria, such as test results.

(b) There shall be an adequate number of qualified personnel to perform the manufacture, processing, packing, or holding of each medical gas.

(c) Only authorized personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

§ 213.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of medical gases shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C--Buildings and Facilities

§ 213.42 Design and construction features.

(a)(1) Any buildings and facilities used in the manufacture, processing, packing, or holding of a medical gas shall be of adequate design, including having adequate space, for the orderly placement of equipment and materials to prevent mix-ups between:

- (i) Components;
- (ii) Incoming designated medical gases;
- (iii) Medical gas containers and closures;
- (iv) Labeling;
- (v) In-process materials; or
- (vi) Medical gases.

(2) Such buildings and facilities shall also allow for adequate cleaning, maintenance, and proper operations.

(b)(1) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:

(i) Receipt, identification, storage, and withholding from use of components, incoming designated medical gases, medical gas containers and closures, and labeling, pending the

appropriate sampling, testing, or examination by the quality unit before release for manufacturing or packaging;

(ii) Holding rejected components, incoming designated medical gases, medical gas containers and closures, and labeling before disposition;

(iii) Storage of released components, incoming designated medical gases, medical gas containers and closures, and labeling;

(iv) Storage of in-process materials;

(v) Manufacturing and processing operations;

(vi) Packaging and labeling operations;

(vii) Quarantine storage before release of medical gases;

(viii) Storage of medical gases after release; and

(ix) Control and laboratory operations.

(2) The flow of components, incoming designated medical gases, medical gas containers and closures, labeling, in-process materials, and medical gases through the buildings and facilities shall be designed to prevent contamination and mix-ups.

(c) Any building or facility used in the manufacture, processing, packing, or holding of a medical gas shall be maintained in a clean condition so as to assure the safety, identity, strength, quality, and purity of the medical gas. Written procedures applicable to the maintenance and cleaning of buildings and facilities shall be established and followed.

Subpart D--Equipment

§ 213.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a medical gas shall be of appropriate design and adequate size, and be suitably located to facilitate operations for its intended use and any necessary cleaning and maintenance.

§ 213.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or medical gases shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, containers, closures, in-process materials, or medical gases so as to alter the safety, identity, strength, quality, or purity of the medical gas beyond the official or other established requirements.

§ 213.67 Equipment maintenance and cleaning.

(a) Written procedures shall be established, maintained, and followed for adequate cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of medical gases. These procedures shall include, but are not necessarily limited to, the following:

- (1) Assignment of responsibility for cleaning and maintaining equipment;
- (2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
- (3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
- (4) Removal or obliteration of previous batch identification;
- (5) Protection of clean equipment from contamination prior to use; and
- (6) Inspection of equipment for cleanliness immediately before use.

(b) The procedures described in paragraph (a) of this section shall not alter the safety, identity, strength, quality, or purity of the medical gas beyond the established requirements.

(c) Records shall be kept of cleaning, maintenance, and inspection as specified in § 213.180.

§ 213.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, and electronic equipment used in the manufacture of medical gases shall be routinely calibrated, inspected, and checked according to a written program designed to ensure proper performance. Written procedures and records of calibration, inspections, and checks shall be maintained.

(b) Computerized systems that record, store, or use data shall be appropriately validated.

(c) A backup file of data entered into the computer system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes.

(d) Appropriate change control shall be used whenever modifications are made to computer systems to assure that any changes do not adversely affect data integrity or product quality. Records of such modifications shall be maintained.

Subpart E--Control of Incoming Designated Medical Gas, Components, and Medical Gas Containers and Closures

§ 213.80 General requirements.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, incoming designated medical gases, and medical gas containers and closures; such written procedures shall be followed.

(b) Components, incoming designated medical gases, and medical gas containers and closures shall at all times be handled and stored in a manner to prevent contamination and mix-ups.

(c) Lots of incoming designated medical gases or components, whether used directly as supply or commingled with an existing supply, shall be assigned a unique identification number.

§ 213.82 Receipt and storage of incoming designated medical gases.

(a)(1) Upon receipt of an incoming designated medical gas, the firm shall verify and record that a signed certificate of analysis from the supplier accompanies each different designated medical gas in a shipment. The certificate of analysis shall include the following:

- (i) Supplier's name;
- (ii) Name of the incoming designated medical gas;
- (iii) Lot number or other unique identification number;
- (iv) Actual analytical result obtained for strength, as well as the results of other tests performed;
- (v) Identification of the test method(s) used for analysis;
- (vi) New drug application and/or new animal drug application number of the incoming designated medical gas; and
- (vii) Supplier representative's signature and the date of signature.

(2) If the incoming designated medical gas is obtained from a supplier other than the original manufacturer, the shipment shall also include complete information from the original manufacturer's certificate of analysis. The firm shall establish and maintain a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures.

(b) An identity test shall be performed upon receipt of the incoming designated medical gas.

§ 213.84 Testing and approval or rejection of components, containers, and closures.

(a) Components, containers, and closures (including valves) shall be examined for conformance with appropriate written procedures and specifications, and approved or rejected, prior to the manufacturing or filling process. In lieu of such examination by the firm, a statement of verification that the component, container, or closure meets specifications may be accepted from the supplier, provided that the firm establishes and maintains a program to ensure the

reliability of the supplier's capabilities through appropriate assessment and testing provisions.

Any rejected items shall be handled in accordance with § 213.89.

(b) Firms shall take appropriate actions to protect against container and closure leaks, which shall include performing leak tests on containers and closures at the time of fill and after fill but prior to release.

(c) Each component shall be sampled, tested, and approved or rejected as appropriate prior to use. This requirement can be met by performing testing for conformance with written specifications or by an identity test on the component accompanied by an acceptable certificate of analysis from the supplier, provided that the firm establishes and maintains a program to ensure the reliability of the supplier's capabilities through appropriate assessment and testing procedures.

§ 213.89 Rejected components, incoming designated medical gases, and medical gas containers and closures.

Rejected components, incoming designated medical gases, and medical gas containers and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable and shall be documented and assessed.

§ 213.94 Medical gas containers and closures.

(a) Medical gas containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the gas beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the medical gas.

(c) Medical gas containers and closures shall be clean to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning shall be written and followed for medical gas containers and closures.

(e) Medical gas containers and closures must meet the following requirements--

(1) *Gas-specific use outlet connections.* Portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver-brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the containers' use) except by the manufacturer. For the purposes of this paragraph, the term "manufacturer" includes any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers. For the purposes of this section, a "portable cryogenic medical gas container" is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, healthcare entity, nursing home, other facility, or home healthcare setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter).

(2) *Gauges for certain medical gas containers.* Portable cryogenic medical gas containers as described in paragraph (e)(1) of this section and small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at § 868.5655 of this chapter) must have a working gauge sufficient to indicate whether the container contains an adequate supply of medical gas for continued use.

(3) *Label and coloring requirements.* The labeling specified at § 201.328(a) of this chapter must be affixed to the container in a manner that does not interfere with other labeling. Each such label as well as materials used for coloring medical gas containers must be reasonably

resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water.

Subpart F--Production and Process Controls

§ 213.100 Written procedures; deviations.

(a) There shall be written procedures for production and process controls designed to assure that medical gases have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

§ 213.101 Charge-in of components and incoming designated medical gases.

Written production and control procedures shall include the following, which are designed to assure that the medical gases produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) Except when a monograph or formulary specifies a range, the batch shall be formulated with the intent to provide 100 percent of the labeled or established amount of each medical gas. When a monograph or formulary specifies a range for the contents of a medical gas, the batch shall be formulated with the intent to provide an amount of the medical gas within such specified range.

(b) Components and incoming designated medical gases added to in-process supply or final product containers shall be weighed or measured as appropriate. In-process and final product containers shall identify the name of the component or designated medical gas or the name and percentage of each component or designated medical gas if they contain multiple components or designated medical gases, and the unique lot number assigned.

§ 213.110 Sampling and testing of in-process materials.

(a) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality unit during the production process.

(b) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes.

(c) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Subpart G--Packaging and Labeling Control

§ 213.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a medical gas.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination, and whether accepted or rejected.

(d) Labels and other labeling materials for each different medical gas, strength, or quantity of contents, shall be stored with suitable identification to avoid mix-ups. Access to the label storage area shall be limited to authorized personnel.

(e) Labels, labeling, and other packaging materials that are obsolete, outdated, or that do not meet applicable requirements shall be destroyed.

(f) Packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different medical gas;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of labeling operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(g) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

(h) Labels may be reused if they are legible, properly affixed to the container, and otherwise meet all applicable requirements.

§ 213.125 Labeling issuance.

(a) Labeling and packaging operations must be controlled to prevent labeling and product mix-ups. Procedures shall be written and followed describing in sufficient detail the control procedures employed for the issuance of labeling.

(b) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of medical gas and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 213.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination

for correct labeling is performed in accordance with § 213.122(f)(2). Labeling reconciliation is also waived for 360° wraparound labels on portable cryogenic medical gas containers.

(c) All excess lot number stickers or decals bearing lot or control numbers shall be discarded.

(d) Bulk or transport containers (as defined in § 201.161(c)(3) of this chapter) are exempt from this section.

§ 213.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for medical gases; such written procedures shall be followed.

These procedures shall incorporate the following features:

(a) Prevention of mix-ups by physical or spatial separation from operations on other products.

(b) Identification and handling of filled containers of medical gas that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the medical gas with a lot or control number that permits determination of the history of the manufacture and control of the batch. The lot or control number of the medical gas may be identified by use of a separate identification sticker or decal.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

Product labels, including 360° wraparound labels, can be reused provided they meet all applicable labeling requirements, all information on the label is legible, and the label is in good condition.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all medical gases have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

(f) Bulk or transport containers (as defined in § 201.161(c)(3) of this chapter) are exempt from this section provided they are identified with the name of the product contained therein and accompanied by documentation identifying the product as meeting applicable compendial standards.

Subpart H--Holding and Distribution

§ 213.150 Warehousing and distribution procedures.

(a) Written procedures shall be established, and followed, describing the distribution of medical gases and including a system by which the distribution of each lot can be readily determined to facilitate its recall if necessary.

(b) Written procedures shall be established, and followed, describing the warehousing of medical gases, including quarantine of such gases before release by the quality unit.

Subpart I--Laboratory Controls

§ 213.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that

components, medical gas containers and closures, in-process materials, labeling, and medical gases conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, medical gas containers and closures, and labeling used in the manufacture, processing, packing, or holding of a medical gas. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for medical gases. Such samples shall be representative and properly identified.

(4) The calibration or verification of calibration for instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

§ 213.165 Testing and release for distribution.

(a) For each batch of medical gas, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the medical gas, including the identity and strength, prior to release.

(b) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling, the number of units per batch to be tested, and acceptance criteria. Such written procedures shall be followed.

(c) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with § 213.194(a)(2). The suitability of all testing methods shall be verified under actual conditions of use.

(d) Medical gases failing to meet established standards or specifications and any other relevant quality criteria shall be rejected.

(e) This section does not apply to the filling of a designated medical gas or medically appropriate combination of designated medical gases via liquid to liquid into a container at a delivery site.

§ 213.166 Stability testing and expiration dating for medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act.

(a) For medical gases marketed under applications submitted under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act, any stability testing performed and any expiration date established shall be in accordance with paragraph (b) of this section, subject to the conditions established in their approved applications, if any.

(b) To assure that the medical gas described in paragraph (a) of this section meets applicable standards of identity, strength, quality, and purity at the time of use:

(1) The stability testing program shall be designed to assess the stability characteristics of the medical gas and its container closure system. The results of stability testing shall be used in determining appropriate storage conditions and any expiration date included on the label. The stability program shall include the appropriate sample size, test intervals, container closure systems, and storage conditions for samples retained for testing.

(2) Any expiration dates included on the label shall appear in accordance with the requirements of § 201.17 of this chapter.

(3) Stability shall be evaluated periodically to ensure that the medical gas continues to meet the standards for identity, strength, quality, and purity stated on the labeling to support the expiration date.

Subpart J--Records

§ 213.180 General requirements.

(a) *Record availability.* All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred and are subject to copying as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(b) *Record requirements.* All records must be legible, stored to prevent deterioration or loss, and original or accurate reproductions of the original records.

(c) *Record retention period.* Except where otherwise provided, all records required to be maintained in compliance with this part must be maintained for a period of at least 3 years after the distribution of the batch of medical gas.

(d) *Maintenance of written records.* Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each medical gas to determine the need for changes in specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch; and

(2) A review of complaints, recalls, returned or salvaged medical gases, and investigations conducted under § 213.192 for each gas.

(e) *Written procedure requirements.* A firm shall establish and follow written procedures to assure that responsible officials of the firm are notified in writing of any recalls, reports of inspectional observations by FDA, regulatory actions related to good manufacturing practices brought by FDA, or investigations resulting from adverse event complaints.

§ 213.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 213.68, just the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

§ 213.184 Records for components, medical gas containers and closures, and labeling.

These records shall include the following:

(a) The results of any test or examination performed (including those performed as required by § 213.84 or § 213.122) and the conclusions derived therefrom.

(b) Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with §§ 213.122 and 213.130.

(c) The disposition of rejected components, medical gas containers and closures, and labeling.

§ 213.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each medical gas shall be prepared, dated, and signed. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product;

(2) A complete list of components and any incoming designated medical gases used in manufacturing designated by names or codes sufficiently specific to indicate any special quality characteristic;

(3) A description of the medical gas containers and closures, and packaging materials and labels; and

(4) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

§ 213.189 Batch production and control records.

(a) Batch production and control records shall be prepared for each batch of medical gas produced.

(b) These records shall include documentation that each significant step in the manufacture, processing, packing, or holding of the medical gas produced was accomplished, including:

(1) Dates and times of each significant step, including in-process and laboratory tests as applicable;

(2) A description of the container for the medical gas, including the number and size of the containers filled as applicable;

(3) Specific identification of each component and its source or in-process material used as applicable;

- (4) Measures of components used in the course of processing as applicable;
- (5) Testing results, including any in-process test results and finished product test results;
- (6) Dated signature or initials of the persons performing and directly supervising or checking each significant event in the operation;
- (7) Inspection of the packaging and labeling area before and after use;
- (8) Complete labeling control records, including specimens or copies of all labeling used and label application and reconciliation records as appropriate;
- (9) Any investigation made according to § 213.192.

§ 213.192 Production record review.

(a) Manufacturing production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality unit to determine compliance with all established, approved written procedures before a batch is released or distributed. The quality unit must review production records to determine whether errors or unexplained discrepancies have occurred prior to batch release. If errors or unexplained discrepancies have occurred, or a batch or any component of the batch fails to meet any of its specifications, the firm must thoroughly investigate and take appropriate corrective actions. A written record of the investigation shall be made and shall include the conclusions and followup.

(b) For production and control records of filling at a delivery site, quality unit review as described in paragraph (a) of this section shall be within one business day after fill.

§ 213.194 Laboratory records.

(a) Laboratory records related to the manufacture of a medical gas must include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample, the batch or lot number to be tested, the date the sample was taken, and the date the sample was tested.

(2) The method used in the testing of the sample, the result of the test, how the results compare with established standards of identity, strength, quality, and purity for the component, container, closure, in-process materials (as applicable), and medical gas tested, a record of any calculations performed in connection with each test and any calculated results, and the unit of measurement of the result for each test. It is not necessary to provide the actual calculation where the result is evident through use of simple addition and subtraction.

(3) Where applicable, any graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or medical gas for each lot tested.

(4) The initials or signature of the person performing the test and the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration or verification of calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 213.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with § 213.166.

§ 213.196 Distribution records.

Distribution records shall contain the name of the product, lot or batch number, name and address of the consignee, and date and quantity shipped. For medical air and medically

appropriate combinations of designated medical gases, the distribution record shall include the percentage of each gas.

§ 213.198 Complaint files.

(a) Written procedures shall be established and followed for the receipt and handling of all written or oral complaints concerning a medical gas. These procedures must include quality unit review of any complaint involving the possible failure of a medical gas to meet any of its specifications and an investigation to determine the cause of the failure. Such procedures shall include provisions for determining the need for an investigation in accordance with § 213.192 as well as determining whether the complaint represents an event that is required to be reported to FDA under part 230 of this chapter.

(b) A written record of each complaint regarding a medical gas must be maintained. The record must include the name of the gas, the lot or batch number, the name of the complainant, the date the complaint was received, the nature of the complaint, and the response to the complaint. It must also include the findings of any investigation and followup. Where an investigation is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

(c) Complaint files shall be maintained in a manner such that they are readily available for inspection by the firm or by FDA during an inspection. Complaint files shall be maintained for at least 1 year after the date the complaint was received or for at least 3 years after distribution of the medical gas, whichever is longer.

Subpart K--Returned and Salvaged Medical Gases

§ 213.204 Returned medical gases.

Returned medical gases shall be identified as such and held. If the conditions under which such returned gases have been held, stored, or shipped before or during their return, or if the condition of the gas, its container, carton, or labeling, as a result of storage or shipping, casts

doubt on the safety, identity, strength, quality, or purity of the gas, the returned gas shall be destroyed unless examination, testing, or other investigations prove the gas meets appropriate standards of safety, identity, strength, quality, or purity. Records of returned medical gases shall be maintained and shall include the name, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned gas. If the reason for a medical gas being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 213.192. Procedures for the holding, testing, and use of returned medical gases shall be in writing and shall be followed. This section is not applicable to the routine refilling of cryogenic medical gas containers in the normal course of business, unless the cryogenic medical gas container was returned due to a quality issue.

§ 213.208 Salvaging of medical gases.

Medical gases in containers that have been subjected to improper storage conditions may be salvaged unless their containers have been subjected to adverse conditions that impact the identity, strength, quality, and purity of the product or integrity of the container closure. Whenever there is a question whether medical gases have been subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory tests that such gases meet all applicable standards of identity, strength, quality, and purity, and the integrity of the container closure system is not compromised. Procedures for the holding, testing, and use of salvaged medical gases shall be in writing and shall be followed.

25. Add part 230 to subchapter C to read as follows:

PART 230--CERTIFICATION AND POSTMARKETING REPORTING FOR DESIGNATED MEDICAL GASES

Sec.

Subpart A--General Provisions

230.1 Scope of this part.

230.2 Purpose.

230.3 Definitions.

Subpart B--Certification of Designated Medical Gases

230.50 General requirements for all submission types.

230.65 Withdrawal by the applicant of a certification request before it is deemed granted.

230.70 Supplements and other changes to a granted certification.

230.72 Change in ownership of a granted certification.

230.80 Annual report.

230.100 FDA review of submissions.

230.105 When a submission is deemed granted.

230.150 Withdrawal or revocation of approval of an application.

Subpart C--Postmarketing Quality and Safety Reporting

230.205 Field alert reports.

230.210 General reporting requirements for designated medical gas adverse events.

230.220 Human designated medical gas ICSR requirements.

230.230 Animal designated medical gas adverse event reporting requirements.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360b, 360cc, 360ddd, 360ddd-1, 371, 374, 379e, 379k-1, 381.

Subpart A--General Provisions

§ 230.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration of certifications to market designated medical gases under sections 575 and 576 of the Federal Food, Drug, and Cosmetic Act, as well as amendments and supplements to those certifications. This part also sets forth the postmarketing safety reporting requirements for designated medical gases.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 230.2 Purpose.

The purpose of this part is to establish an efficient process for the certification of designated medical gases and to establish an effective system for surveillance of such gases.

§ 230.3 Definitions.

(a) The definitions and interpretations contained in sections 201 and 575 of the Federal Food, Drug, and Cosmetic Act apply to those terms when used in this part of this chapter.

(b) The following definitions of terms apply to this part:

(1) *Adverse event* means any untoward medical occurrence associated with the use of a designated medical gas in humans or animals, whether or not it is considered related to the designated medical gas. An adverse event can occur in the course of the use of a designated medical gas; from overdose of a designated medical gas, whether accidental or intentional; from abuse of a designated medical gas; from discontinuation of the designated medical gas (e.g., physiological withdrawal); and it includes any failure of expected pharmacological action.

(2) *Applicant* means any person or entity who submits a certification request for a designated medical gas under this part, including a supplement, and any person or entity who owns a granted certification for a designated medical gas under this part.

(3) *Certification request* means a submission under section 576 of the Federal Food, Drug, and Cosmetic Act requesting certification of a medical gas as a designated medical gas.

(4) *FDA or Agency* means the Food and Drug Administration.

(5) *Individual case safety report (ICSR)* means a description of an adverse event related to an individual patient or subject.

(6) *ICSR attachments* means documents related to the adverse event described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

(7) *Life-threatening adverse event* means any adverse event that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse event as it occurred, i.e., it does not include an adverse event that, had it occurred in a more severe form, might have caused death.

(8) *Minimum data set for an ICSR for an adverse event* means the minimum four elements required for reporting an ICSR of an adverse event: An identifiable patient, an identifiable reporter, a suspect designated medical gas, and an adverse event.

(9) *Nonapplicant* means any person other than the applicant whose name appears on the label of a designated medical gas container as a manufacturer, packer, or distributor.

(10) *Serious adverse event* means:

(i) An adverse event is considered “serious” if it results in any of the following outcomes:

(A) Death;

(B) A life-threatening adverse event;

(C) Inpatient hospitalization or prolongation of existing hospitalization;

(D) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; and/or

(E) A congenital anomaly/birth defect.

(ii) Other events that may be considered serious adverse events: important medical events that may not result in one of the listed outcomes in this definition may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or study subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include: allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of product dependency or product abuse.

Additional examples in animals include: severe hypersensitivity reactions or respiratory distress.

Subpart B--Certification of Designated Medical Gases

§ 230.50 General requirements for all submission types.

(a) Who must submit a request for certification.

(1) The certification process described in this subpart applies to designated medical gases for the indications described in section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act. Any person who seeks to initially introduce or deliver for introduction a designated medical gas into interstate commerce shall file a request for certification. The certification process is the same for all designated medical gases, regardless of whether it is intended for human use, animal use, or both. The applicant must identify its intention to market its designated medical gas for human use, animal use, or both.

(2) Any person that proposes to market a medical gas that is a new drug for human use must obtain approval under part 314 of this chapter, and any person that proposes to market a medical gas that is a new animal drug for animal use must obtain approval under part 514 of this chapter, unless--

(i) The medical gas meets the definition of a designated medical gas; and

(ii) The medical gas is proposed to be marketed:

(A) Alone, or

(B) In combination (as medically appropriate) with another designated medical gas or other designated medical gases; and

(C) For which a certification or certifications have been granted, for a use described under section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act.

(b) The applicant must include the following information in its certification request:

(1) *Applicant information.* The applicant must identify the name, address, telephone number, and email address of the person or entity requesting certification. If the address of the entity requesting certification is not in the United States, the certification request is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *Type of submission.* The applicant must indicate the type of submission as one of the following:

(i) Original Certification Request--An initial request submitted by an applicant for certification of a medical gas as a designated medical gas.

(ii) Amendment to a Pending Certification Request--Any submission related to a pending submission that revises existing information or provides additional information, including responses to Information Request Letters.

(iii) Resubmission--Any submission that has been revised and submitted again following a previous denial. If an applicant chooses to resubmit its submission, it must provide a written response to the deficiencies identified in FDA's denial letter, along with other information required for certification requests.

(iv) Supplement to a granted certification--Any submission that contains a change to a granted certification.

(v) Other--Any submission that does not fit in one of the other categories.

(3) *Description of medical gas.* A separate certification request is required to be submitted for each designated medical gas for which certification is sought. Each designated medical gas certification request must include the name of the medical gas and a certification statement from the applicant that the designated medical gas meets the appropriate compendial standard.

(4) *Facility information.* Each certification request must include the name and address of the facility or facilities where the designated medical gas will be initially produced. For each facility, include a brief description of the manufacturing or processing activities performed, the FDA Establishment Identifier (FEI), if one exists, and the Unique Facility Identifier in accordance with the requirements of part 207 of this chapter and section 510 of the Federal Food, Drug, and Cosmetic Act. For amendments and supplements, only changes to the list of facilities are required to be included.

(5) *Certification of adequate manufacture, processing, packaging, and holding of designated medical gas.* The applicant must certify that the applicant's methods, facilities, and controls used for the manufacture, processing, packing, and holding of the designated medical gas, as applicable, are adequate to ensure its safety, identity, strength, quality, and purity.

(6) *Additional information.* The applicant must provide any other information which FDA deems appropriate to determine whether the medical gas is a designated medical gas. The applicant may also provide other information that the applicant believes will assist FDA in evaluating the request.

(c) *Where and how to submit a request for certification.* The applicant must submit a signed, completed request for certification form either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705.

§ 230.65 Withdrawal by the applicant of a certification request before it is deemed granted.

An applicant may at any time withdraw a certification request that is not yet deemed granted by notifying FDA in writing. A decision to withdraw the certification request is without prejudice to refile. The Agency will retain the certification request and will provide a copy to the applicant on request under the fee schedule in § 20.45 of this chapter (FDA's public information regulations).

§ 230.70 Supplements and other changes to a granted certification.

(a) The applicant must submit a supplement if any information in the certification request changes after the request has been deemed granted, including, but not limited to, the addition of a new facility manufacturing the designated medical gas, a change in contact information, or a change in the corporate name.

(b) Each supplement must include a signed, completed request for certification form with the updated information in accordance with § 230.50. The updated information must be submitted no later than 30 calendar days after the date the change occurred.

§ 230.72 Change in ownership of a granted certification.

An applicant may transfer ownership of its certification. At the time of transfer the new and former owners are required to submit information to FDA as follows:

(a) The former owner must submit a letter or other document that states that all rights to the certification have been transferred to the new owner.

(b) The new owner must submit a supplement under § 230.70 signed by the new owner describing any changes in the conditions in the granted certification and a letter or other document containing the date that the change in ownership is effective.

§ 230.80 Annual report.

(a) The applicant must submit each year within 60 calendar days of the anniversary of the date the certification was deemed granted, an annual report containing the information described in paragraph (b) of this section. The applicant must submit a signed, completed annual report form either in an electronic format that FDA can process, review, and archive, or in hard copy by submitting two paper copies to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705.

(b) The report must contain, for the prior 12 months, the following information in the order listed:

(1) *Summary.* A brief summary of significant new information that might affect the safety, effectiveness, or labeling of the designated medical gas, including any actions the applicant has taken or intends to take as a result of this new information.

(2) *Distribution data.* Information about the quantity of the designated medical gas distributed by the applicant. The information must include the National Drug Code (NDC)

numbers and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(3) *Administrative changes.* Any changes to the applicant's name or contact information.

(4) *Current facilities.* A list of current facilities, and a list of facilities that are no longer in use.

§ 230.100 FDA review of submissions.

(a) In reviewing a submission pursuant to § 230.50, FDA will consider information provided with the submission along with any other available, relevant information of which FDA becomes aware, including information obtained from State or Federal officials, FDA inspection reports, or any other source.

(b) FDA will deny a submission if FDA finds that:

(1) The medical gas that is the subject of the submission is not a designated medical gas;

(2) The submission does not contain the required information or otherwise appears to lack sufficient information to determine that the medical gas is a designated medical gas;

(3) The applicant's methods, facilities, and controls used for the manufacture, processing, and handling of the designated medical gas, as applicable, are not adequate to ensure its safety, identity, strength, quality, and purity; or

(4) Denying the request is otherwise necessary to protect the public health.

(c) Within 60 calendar days of filing of a submission, FDA may contact the applicant to request additional information regarding the submission if it determines that required information is not included in the submission, that FDA needs such information to determine whether the medical gas is a designated medical gas, or that FDA determines such information is necessary to protect the public health. Upon receipt of an amendment to a pending certification request, this 60-day review period will restart. If FDA is not able to contact the applicant to obtain and evaluate the information within the 60-day review period, FDA may find that the submission lacks sufficient information to permit a determination that the medical gas is a

designated medical gas and deny the submission. If FDA is able to contact the applicant but is not provided with the additional information requested within the 60-day review period, FDA may find that the request lacks sufficient information to permit a determination that the medical gas is a designated medical gas and deny the submission.

(d) Within 60 calendar days of filing of a submission, if FDA makes one of the findings described in § 230.100(b), FDA will notify the applicant in writing that the submission is denied and provide the basis for FDA's determination.

§ 230.105 When a submission is deemed granted.

Unless FDA makes one of the findings described in § 230.100(b) and notifies the applicant within 60 calendar days of filing that the submission is denied, the certification is deemed to be granted and the designated medical gas will be deemed to have in effect an approved application under section 505 or section 512 of the Federal Food, Drug, and Cosmetic Act, or both, as applicable, for the indications described in section 576(a)(3)(A)(i) of the Federal Food, Drug, and Cosmetic Act. FDA will notify the applicant in writing.

§ 230.150 Withdrawal or revocation of approval of an application.

(a) Withdrawal.

(1) FDA will notify the applicant, and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in §§ 314.200, 514.200, or both, as applicable, if any of the following apply:

(i) The Secretary of Health and Human Services has suspended the approval of the application for a designated medical gas on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(ii) FDA finds:

(A) That clinical or other experience, tests, or other scientific data show that the designated medical gas is unsafe for use under the conditions of use upon the basis of which the application was approved; or

(B) That new evidence of clinical experience not available to FDA until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the designated medical gas is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(C) Upon the basis of new information before FDA with respect to the designated medical gas, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126 of this chapter, that the designated medical gas will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(D) That the application contains any untrue statement of a material fact.

(2) FDA may notify the applicant, and afford an opportunity for a hearing on a proposal to withdraw approval of the application under the procedure in §§ 314.200, 514.200, or both, as applicable, if the Agency finds:

(i) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports applicable to designated medical gases, including under sections 505(k) and 512(l) of the Federal Food, Drug, and Cosmetic Act and this part and part 213 of this chapter, or that the applicant has refused to permit access to, or copying or verification of, its records.

(ii) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the designated medical gas are

inadequate to ensure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Agency.

(iii) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the labeling of the designated medical gas, based on a fair evaluation of all material facts, is false or misleading in any particular, and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the Agency.

(iv) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the Federal Food, Drug, and Cosmetic Act.

(3) FDA will withdraw approval of an application if the applicant requests its withdrawal because the designated medical gas subject to the application is no longer being marketed, provided none of the conditions listed in paragraphs (a)(1) and (2) of this section applies to the designated medical gas. FDA will consider a written request for a withdrawal under this clause to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application under this clause is without prejudice to refiling.

(4) FDA may notify an applicant that it believes a potential problem associated with a designated medical gas is sufficiently serious that the designated medical gas should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the Agency will not make a finding under paragraph (a) of this section, but will withdraw approval of the application in a notice published in the *Federal Register* that contains a brief summary of the Agency's and the applicant's views of the reasons for withdrawal.

(5) If FDA withdraws an approval, FDA will publish a notice in the *Federal Register* announcing the withdrawal of approval.

(b) *Revocation.* FDA may revoke the grant of a certification if FDA determines, after providing the applicant with notice and opportunity for an informal hearing in accordance with part 16 of this chapter, that the request for certification contains any material omission or falsification.

Subpart C--Postmarketing Quality and Safety Reporting

§ 230.205 Field alert reports.

The applicant shall submit all information described in paragraphs (a) and (b) of this section about distributed designated medical gases and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: “Designated Medical Gas--Field Alert Report.”

(a) Information concerning any incident that causes the designated medical gas or its labeling to be mistaken for, or applied to, another article.

(b) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed designated medical gas, or any failure of one or more distributed batches of the designated medical gas to meet established specifications.

§ 230.210 General reporting requirements for designated medical gas adverse events.

(a) *Review of safety information.* Each applicant and nonapplicant must promptly review all safety information that the applicant or nonapplicant receives or otherwise obtains from any source, foreign or domestic, such as information derived from commercial marketing experience, reports in the published scientific and medical literature, unpublished scientific papers, and reports from regulatory authorities.

(b) *Safety reporting disclaimer.* (1) A report or information submitted by an applicant or nonapplicant (and any release by FDA of that report or information) under § 230.220 or 230.230

does not necessarily reflect a conclusion by the applicant or nonapplicant or by FDA that the report or information constitutes an admission that the designated medical gas caused or contributed to an adverse effect.

(2) An applicant or nonapplicant need not admit, and may deny, that the report or information submitted under § 230.220 or 230.230 constitutes an admission that the designated medical gas caused or contributed to an adverse effect.

§ 230.220 Human designated medical gas ICSR requirements.

(a) *ICSR Reporting.* (1) *General.* Except as provided in paragraph (c) of this section, applicants and nonapplicants must submit each ICSR associated with the use of a designated medical gas in humans described in paragraph (b) of this section to FDA as soon as possible but no later than 15 calendar days from the date when the applicant or nonapplicant has both met the reporting criteria described in paragraph (b) of this section and acquired a minimum data set for an ICSR for that adverse event.

(2) *Copies of ICSRs obtained from FDA.* An applicant or nonapplicant should not resubmit under this section any ICSRs obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA.

(3) *Followup information.* Applicants and nonapplicants must submit any new information that is related to a previously submitted ICSR or an ICSR that was sent to the applicant by FDA no later than 15 calendar days after the information is received or otherwise obtained.

(b) *Reporting requirements.* (1) *Serious adverse events.*

(i) *Reported spontaneously.* Applicants and nonapplicants must submit ICSRs for serious adverse events reported to the applicant or nonapplicant spontaneously (such as a report initiated by a patient, consumer, or healthcare professional).

(ii) *Reported from the scientific literature.* Applicants and nonapplicants must submit ICSRs for serious adverse events obtained from published scientific and medical journals either as case reports or as the result of a formal clinical trial.

(iii) *Exception to reporting requirements for serious adverse events.* Notwithstanding paragraph (b)(1)(i) and (ii) of this section, ICSRs are not required for reports of the death of a patient who was administered oxygen, unless the applicant or nonapplicant is aware of evidence to suggest that the death was caused by the administration of oxygen.

(2) *Other adverse event reports to be submitted upon notification by FDA.* Upon notification by FDA, applicants and nonapplicants must submit, in a timeframe established by FDA, ICSRs for any adverse event that are not required under paragraph (b)(1) of this section. The notification will specify the adverse events to be reported and the reason for requiring the reports.

(c) *Completing and submitting ICSRs.* This paragraph describes how to complete and submit ICSRs required under this section.

(1) *Electronic format for submissions.*

(i) ICSRs and ICSR attachments must be in an electronic format that FDA can process, review, and archive, as described in § 314.80(g)(1) of this chapter.

(ii) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (c)(1)(i) of this section, as described in § 314.80(g)(2). These waivers will be granted on a limited basis for good cause shown.

(2) *Submitting ICSRs.*

(i) *Single submission of each ICSR.* Submit each ICSR only once.

(ii) *Separate ICSR for each patient.* The applicant or nonapplicant must submit a separate ICSR for each patient who experiences an adverse event reportable under paragraph (b) of this section.

(iii) *Coding terms.* The adverse event terms described in the ICSR must be coded using standardized medical terminology.

(iv) *Minimum data set.* All ICSRs submitted under this section must contain at least the minimum data set for an ICSR for an adverse event. The applicant or nonapplicant must actively seek the minimum data set in a manner consistent with the written procedures under paragraph (f) of this section. Applicants and nonapplicants must document and maintain records of their efforts to obtain the minimum data set.

(v) *ICSR elements.* The applicant or nonapplicant must complete all known, available elements of an ICSR as specified in paragraph (d) of this section.

(A) For adverse events, applicants and nonapplicants must actively seek any information needed to complete all applicable elements, consistent with their written procedures under paragraph (f) of this section.

(B) Applicants and nonapplicants must document and maintain records of their efforts to obtain the missing information.

(vi) *Supporting documentation.* An applicant or nonapplicant must submit the following types of supporting documentation in an ICSR, if available:

(A) A copy of the autopsy report if the patient died, or a copy of the hospital discharge summary if the patient was hospitalized. The applicant or nonapplicant must submit each document as an ICSR attachment. The ICSR attachment must be submitted either with the initial ICSR or no later than 15 calendar days after obtaining the document. English translations of foreign language documents must be provided.

(B) A copy of the published article as an ICSR attachment for each ICSR of an adverse event obtained from the published scientific and medical literature. Foreign language articles must be accompanied by an English translation of the abstract. When submitting more than one ICSR from the same published article, the applicant or nonapplicant must submit only one copy of the article with one of the ICSRs. For the remaining ICSRs not accompanied by a copy of the

published article, the applicant or nonapplicant must include the cross-reference to the specific ICSR to which the article is attached.

(d) *Information reported on ICSRs.* ICSRs must include the following information, subject to paragraph (c)(2)(v) of this section:

(1) Patient information, which includes:

- (i) Patient identification code;
- (ii) Patient age at the time of adverse event, or date of birth;
- (iii) Patient gender; and
- (iv) Patient weight.

(2) Adverse event, which includes:

- (i) Outcome attributed to adverse event;
- (ii) Date of adverse event;
- (iii) Date of ICSR submission;
- (iv) Description of adverse event;
- (v) Adverse event term(s);
- (vi) Description of relevant tests conducted, including dates and laboratory data; and
- (vii) Other relevant patient history, including preexisting medical conditions.

(3) Suspect designated medical gas(es), which includes:

- (i) Name;
- (ii) Dose, frequency, and route of administration used;
- (iii) Therapy dates;
- (iv) Diagnosis for use (indication);
- (v) Whether the adverse event abated after the use of the designated medical gas(es)

stopped or the dose was reduced;

(vi) Whether the adverse event reappeared after reintroduction of the designated medical gas(es);

(vii) Lot number;

(viii) National Drug Code (NDC) number; and

(ix) Concomitant medical products and therapy dates.

(4) Initial reporter information, which includes:

(i) Name, address, email address, and telephone number;

(ii) Whether the initial reporter is a healthcare professional; and

(iii) Occupation, if a healthcare professional.

(5) Applicant or nonapplicant information, which includes:

(i) Applicant or nonapplicant name, address, email address, and telephone number;

(ii) Report source, such as spontaneous, literature, or study;

(iii) Date the report was received by applicant or nonapplicant;

(iv) New drug application and/or new animal drug application number;

(v) Whether the ICSR is an expedited report;

(vi) Whether the ICSR is an initial report or followup report; and

(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(e) *Recordkeeping.*

(1) For a period of 10 years from the initial receipt of information, each applicant or nonapplicant must maintain records of information relating to adverse events under this section, whether or not submitted to FDA.

(2) These records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant.

(3) Upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or

nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records described in this section.

(f) *Written procedures.* The applicant or nonapplicant must develop written procedures needed to fulfill the requirements in this section for the surveillance, receipt, evaluation, and reporting to FDA of adverse event information, including procedures for employee training and for obtaining and processing adverse event information from other applicants and nonapplicants.

(g) *Patient privacy.* An applicant or nonapplicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant or nonapplicant should assign a unique code for identification of the patient. The applicant or nonapplicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. As set forth in FDA's public information regulations in part 20 of this chapter, FDA generally may not disclose the names of patients, individual reporters, healthcare professionals, hospitals, and geographical identifiers submitted to FDA in adverse event reports.

§ 230.230 Animal designated medical gas adverse event reporting requirements.

(a) *Report for adverse events.* This report provides information on each adverse event associated with the use of a designated medical gas in animals, regardless of the source of the information.

(1) *Serious adverse events.* The applicant or nonapplicant must submit serious adverse events to FDA as soon as possible but no later than within 15 calendar days of first receiving the information. The report must be submitted to the Agency in electronic format as described in paragraph (b)(1) of this section, unless the applicant or nonapplicant obtains a waiver under paragraph (b)(2) of this section or FDA requests the report in an alternate format.

(i) *Reported spontaneously.* Applicants and nonapplicants must submit reports for *each serious adverse event* reported to the applicant or nonapplicant spontaneously (such as reports initiated by a patient, consumer, veterinarian, or other healthcare professional), regardless of

whether the applicant or nonapplicant believes the events are related to the designated medical gas.

(ii) *Reported from the scientific and medical literature.* Applicants and nonapplicants must submit reports for each serious adverse event obtained from the published scientific and medical literature regardless of whether the applicant or nonapplicant believes the events are related to the designated medical gas.

(iii) *Exception to reporting requirements for serious adverse events.* Notwithstanding paragraphs (a)(1)(i) and (ii) of this section, reports are not required to be submitted for the death of an animal that was administered oxygen, unless the applicant or nonapplicant becomes aware of evidence to suggest that the death was caused by the administration of oxygen.

(2) *Other adverse event reports to be submitted upon notification by FDA.* Upon notification by FDA, applicants and nonapplicants must submit reports of adverse events associated with the use of a designated medical gas in animals that do not qualify for reporting under paragraph (a)(1) of this section. The notice will specify the adverse events to be reported and the reason for requiring the reports.

(3) *Copies of adverse event reports obtained from FDA.* An applicant or nonapplicant should not resubmit under this section any adverse event reports obtained from FDA's adverse event reporting database or forwarded to the applicant or nonapplicant by FDA.

(b) *Format for submissions.*

(1) *Electronic submissions.* Reports submitted to FDA under this section must be submitted in an electronic format that FDA can process, review, and archive. Data provided in electronic submissions must be in conformance with the data elements in Form FDA 1932 and FDA technical documents describing transmission. As necessary, FDA will issue updated technical documents on how to provide the electronic submission (e.g., method of transmission and processing, media, file formats, preparation and organization of files). Unless requested by FDA, paper copies of reports submitted electronically should not be submitted to FDA.

(2) *Waivers.* An applicant or nonapplicant may request, in writing, a temporary waiver of the electronic submission requirements in paragraph (b)(1) of this section. The initial request may be provided by telephone or email to CVM's Division of Veterinary Product Safety, with prompt written followup submitted as a letter to the granted certification(s). FDA will grant waivers on a limited basis for good cause shown. If FDA grants a waiver, the applicant or nonapplicant must comply with the conditions for reporting specified by FDA upon granting the waiver.

(c) *Records to be maintained.*

(1) For a period of 5 years from the initial receipt of information, each applicant or nonapplicant must maintain records of information relating to adverse event reports under this section, whether or not submitted to FDA.

(2) These records must include raw data, correspondence, and any other information relating to the evaluation and reporting of adverse event information that is received or otherwise obtained by the applicant or nonapplicant.

(3) Upon written notice by FDA, the applicant or nonapplicant must submit any or all of these records to FDA within 5 calendar days after receipt of the notice. The applicant or nonapplicant must permit any authorized FDA employee, at reasonable times, to access, copy, and verify these established and maintained records described in this section.

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

26. The authority citation for part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 360ddd, 360ddd-1, 371, 374, 379e, 379k-1.

27. In § 314.1, redesignate paragraph (c) as paragraph (d) and add new paragraph (c) to read as follows:

§ 314.1 Scope of this part.

(c) The following provisions do not apply to designated medical gases, which are subject to the certification and postmarketing reporting requirements under part 230 of this chapter:

- (1) §§ 314.50 through 314.72;
- (2) § 314.80 except paragraph (g);
- (3) § 314.81(a), (b)(1), and (b)(2);
- (4) § 314.90;
- (5) Subpart C;
- (6) §§ 314.100 through 314.162;
- (7) Subpart H; and
- (8) Subpart I.

PART 514--NEW ANIMAL DRUG APPLICATIONS

28. The authority citation for part 514 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 354, 356a, 360b, 360ccc, 360ddd, 360ddd-1, 371, 379e, 381.

29. In § 514.1, add an eighth sentence to the end of paragraph (a) to read as follows:

§ 514.1 Applications.

(a) ***The following provisions do not apply to designated medical gases, which are subject to the certification requirements under part 230 of this chapter: §§ 514.1(b) through 514.8, 514.12, and 514.15; and Subpart B.

30. Amend § 514.80 by:

- a. In the intro text table adding a new entry after the sixth row.
- b. Adding a new paragraph (a)(6).

The additions read as follows.

§ 514.80 Records and reports concerning experience with approved new animal drugs.

The following table outlines the purpose for each paragraph of this section:

Purpose	21 CFR Paragraph and Title

Does this section apply to designated medical gases subject to the certification requirements under part 230?	514.80(a)(6).

(a) ***

(6) This section does not apply to designated medical gases, which are subject to the certification requirements under part 230 of this chapter. Part 230 of this chapter contains requirements related to records and reports concerning experience with the use of a designated medical gas in animals.

Dated: May 9, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

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